26.7.78

July 1973

THE BRITISH JOURNAL OF RADIOLOGY

5

CUK-H06082-5-P25838

X-ray diagnosis
Radiation oncology
Nuclear medicine
Ultrasound
Radiological physics
Radiobiology
Radiation protection
and related disciplines

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

Published by
The British Institute of Radiology

The British Journal of Radiology

FOUNDED 1896

The Editorial Committee consists of:

The Editors:

D. K. BEWLEY, M.A., PH.D. F. STARER, F.R.C.P., F.R.C.R.

The Deputy Editors:

B. T. HALE, M.B., CH.B., F.R.C.R., D.M.R.T. N. W. RAMSEY, PH.D., F.INST.P.

J. ROYLANCE, F.R.C.R.

and

The Associate Editors:

A. B. AYERS, M.D., D.M.R.D., F.R.C.R.
THELMA D. BATES, M.B., CH.B., F.R.C.R., D.C.R.A.
D. COSGROVE, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. COTTRALL, B.A., M.SC., PH.D., F.INST.P.
C. D. R. FLOWER, M.A., F.R.C.P.(C), F.R.C.R.
N. E. GILLIES, B.SC., PH.D.
J. A. GLEESON, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
H. GRAVELLE, B.SC., M.B., CH.B., F.R.C.P.(E.), F.R.C.R., D.M.R.D.
J. L. HAYBITTLE, M.A., PH.D.
C. R. HILL, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. KEELING, M.A., M.SC., M.B.
I. KELSEY FRY, D.M., F.R.C.P., F.R.C.R.
B. KENDALL, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. MEIRE, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. PATTON, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. SCOTT, M.D.
T. SHERWOOD, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. VEALL, D.SC., F.INST.P.

The Associate Editors Overseas are:

P. ARMSTRONG, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
J. R. CUNNINGHAM, M.SC., PH.D. (Canada)
H. A. LUKE, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. SIM, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. STANFORD, M.A., F.INST.P. (Australia)

Managing Editor: MRS. LEE SURRY

Communications should be addressed to the Editors in accordance with the Instructions to Authors which are published in the January issue of the Journal in each year and copies of which may be obtained on application to the Managing Editor.

ADVERTISEMENTS: Communications regarding accounts should be addressed to the Institute. All other communications should be addressed to Miss Hilary Cook, Advertising Manager, The British Journal of Radiology, Advertisement Department, 24a Litchfield Street, London WC2H 9NX.

SUBSCRIPTIONS: All communications should be sent to The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England. Notification of change of address should include an old mailing label and the new address. Claims for missing copies can only be allowed if received within three months of publication date.

ANNUAL SUBSCRIPTION: (post free, payable in advance) £35·00 per annum (monthly) (U.S.A. $65). Single copies: £3·50.

Second class postage paid at New York. Mailing agents: N.Y. Expediters of the Printed Word Ltd., 527 Madison Avenue, Suite 1217, New York, N.Y. 10022, U.S.A.

The British Institute of Radiology

Incorporated by Royal Charter
Founded 1897

P25838

32 WELBECK STREET, LONDON W1M 7PG
Telephone: 01-935 6237 and 01-935 6867. Cable Address: "Britology, London W.1."

President: J. F. FOWLER, D.SC., PH.D., F.INST.P.

Hon. Secretaries:

W. HATELY, M.B., CH.B., F.R.C.P.E., F.R.C.R., D.M.R.D. P. N. T. WELLS, M.SC., PH.D., F.INST.P.

Hon. Treasurer: D. T. KERRISK

THE BRITISH INSTITUTE OF RADIOLOGY is an association of persons interested in Radiology and allied subjects. Meetings are held monthly from October until May. Particulars of membership and other information may be obtained on application to the General Secretary at the Institute.

© British Institute of Radiology, 1978

The British Journal of Radiology

FOUNDED 1896

New Series

VOLUME 51

JANUARY TO DECEMBER, 1978

The Editorial Committee consists of:

The Editors:

D. K. Bewley, M.A., PH.D
F. Starer, F.R.C.P., F.R.C.R.

The Deputy Editors:

B. T. Hale, M.B., CH.B., F.R.C.R., D.M.R.T.
N. W. Ramsey, PH.D., F.INST.P.
J. Roylance, F.R.C.R.

and
The Associate Editors:

A. B. Ayers, M.D., D.M.R.D., F.R.C.R.
Thelma D. Bates, M.B., CH.B., F.R.C.R., D.C.R.A.
D. Cosgrove, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. Cottrall, B.A., M.SC., PH.D.
R. Dick, M.B., B.S., M.R.A.C.R., F.R.C.R.
C. D. R. Flower, M.A., F.R.C.P.(C), F.R.C.R.
N. E. Gillies, B.SC., PH.D.
J. A. Gleeson, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
H. Gravelle, B.SC., M.B., CH.B., F.R.C.R., D.M.R.D.
J. L. Haybittle, M.A., PH.D.
C. R. Hill, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. Keeling, M.A., M.SC., M.B.
I. Kelsey Fry, D.M., F.R.C.P., F.R.C.R.
B. Kendall, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. Meire, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. Patton, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. Scott, M.D.
T. Sherwood, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. Veall, D.SC., F.INST.P.

The Associate Editors Overseas are:

P. Armstrong, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
B. J. Cremin, F.R.A.C.R., F.R.C.R. (South Africa)
J. R. Cunningham, M.SC., PH.D. (Canada)
H. A. Luke, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. Sim, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. Stanford, M.A., F.INST.P. (Australia)

Managing Editor: Mrs. Lee Surry

Published by
THE BRITISH INSTITUTE OF RADIOLOGY
32 Welbeck Street, London W1M 7PG

© British Institute of Radiology, 1978

INDEX TO AUTHORS

1978

Abadir, R., Edward, M., 653
Ackery, D. M., Garvie, N. W., Harrison, G. S. M., 825
Adams, F. G., Horton, P. W., 281
Adams, G. E., Stratford, I. J., 745
Addy, R. W., 397
Agnew, J. E., Maze, M., 206
Ahier, R. G., Law, Marilyn P., Field, S. B., 132
Al Jarallah, M. I., Archer-Hall, J. A., Francois, P., E., 392, 821
Alper, Tikvah, 399
Amin, P. H., Evans, A. N. W., 539
Amols, H. I., Bain, E., Carpenter, S. G., Cox, R. A., Robertson, J. B., Raju, M. R., 712
Amols, H. I., Dicello, J. F., Graves, R. U., Howard, J., Koehler, A. M., Lyman, J. T., Raju, M. R., Smathers, J. B., 699
Amplatz, K., Edwards, J. E., Casteneda-Zuniga, W. R., 633
Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Andrew, E. R., Bottomley, P. A., Hinshaw, W. S., Holland, G. N., Moore, W. S., Worthington, B. S., 273
Andrews, J. T., Smidt, K. P., 50
Archer-Hall, J. A., Al-Jarallah, M. I., Francois, P. E., 392, 821
Ardran, G. M., Birch, R., Crooks, H. E., 867
Ardran, G. M., Brodribb, A. J. M., Fursdon, P. S., Gear, J. S. S., Nolan, D. J., 472
Ardran, G. M., Crooks, H. E., 29
Ardran, G. M., Dixon-Brown, A., Fursdon, P. S., 210
Armstrong, P., Chalmers, A. H., Green, G., Irving, J. D., 333
Ashcroft, M. T., Walker, T. M., 338
Ashley, A. J., Phelps, P. D., 437

Baarli, J., Bianchi, Marilena, Hill, C. K., Sullivan, A. H., 127
Bahk, Y. W., Kim, C. Y., 847
Bain, E., Amols, H. I., Carpenter, S. G., Cox, R. A., Robertson, J. B., Raju, M. R., 712
Bain, E., Carpenter, S. G., Cox, R. A., Raju, M. R., Robertson, J. B., 704
Balk, O. A., Hochhäuser, E., 460
Banks, R. A., Riordan, J. F., Rudolf, M., Saunders, K. B., 286
Banna, M., 738
Barnes, N. R., Boulis, Z. F., Dick, R., 851
Barrett, J. J., Clarke, M. B., Howard, E. R., Jenner, R. E., 858, 862
Bazzocchi, M., Dalla Palma, L., di Pietrantonio, M., 484
Beddoe, A. H., Spiers, F. W., Whitwell, Joan, R., 622
Beggs, I., 918
Bell, G. D., Doran, J., McAllister, J., McMullin, J., Monks, A., Oliver, J., Richens, A., 251
Bell, G. D., Fayadah, M., Frank, J., Kelsey Fry, I., McMullin, J., 111
Bell, G. D., Fayadah, M., Frank, J., Kelsey Fry, I., Smith, P. L. C., 191
Bell, G. D., McAllister, J., McMullin, J., Oliver, J., 17
Berridge, F. R., Dick, A. P., Freeman, A. H., Gleeson, J. A., Zeegen, R., 782
Best, J. K., Khan, A. R., Lavender, J. P., 51
Bewley, D. K., Page, B. C., 375
Bhatia, D. P., Nagarajan, P. S., 223
Bianchi, Marilena, Baarli, J., Hill, C. K., Sullivan, A. H., 127
Bingham, J. B., Hilson, A. J. W., Maisey, M. N., 342
Bingham, J. B., Maisey, M. N., 599
Birch, R., Ardran, G. M., Crooks, H. E., 867
Bleehen, N., Anderson, P., Dische, S., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Bloomer, W. D., Chaffey, J. T., Dritschilo, A., Marck, A., 370
Boldero, J. L., 829
Bolin, F. P., Preuss, L. E., 750
Bottomley, P. A., Andrew, E. R., Hinshaw, W. S., Holland, G. N., Moore, W. S., Worthington, B. S., 273
Boulis, Z. F., Barnes, N. R., Dick, R., 851
Bowring, C. S., Keeling, D. H., 836
Braganza, J. M., Fawcitt, R. A., Forbes, W. St. C., Howat, H. T., Isherwood, I., 1
Bresnihan, E., de Dombal, F. T., Fakes, S., Horrocks, J., Parkin, G. J. S., Smith, S. E. W., 528
Brindle, J., Bleehen, N. M., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
British Nuclear Medicine Society, (Croft, D. H.), 59
Brochier, M., Itti, R., Pellois, A., Planiol, T., 443
Brock, L. G., 822
Brodey, P. A., Fisch, A. E., Mall, J. C., Salman, B. J., 688
Brodribb, A. J. M., Ardran, G. M., Fursdon, P. S., Gear, J. S. S., Nolan, D. J., 474
Broerse, J. J., Mijnheer, B. J., Zoetelief, J., 122
Brustad, T., Rofstad, E. K., 381
Bryant, T. H. E., Julian, W. L., 974
Bullimore, J., Bleehen, N. M., Brindle, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Bunton, R. W., Grennan, D. M., Palmer, D. G., de Silva, R. T. D., 963
Burch, P. R. J., 398
Burrows, E. H., 771
Burrows, E. H., Johnson, A. J., 196
Bush, R. S., Hill, R. P., Siemann, D. W., 992

Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D., Saunders, M. I., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
Calne, R. Y., Machell, R. J., 631
Campbell, A., 925

INDEX TO AUTHORS—continued

Cannell, L. B., Park, W. M., Timothy, A. R., Tucker, Audrey K., 328
Cargill, A., Hately, W., 910
Carmichael, J. H. E., Warrick, C. K., 843
Carpenter, S. G., Amols, H. I., Bain, E., Cox, R. A., Robertson, J. B., Raju, M. R., 712
Carpenter, S. G., Bain, E., Cox, R. A., Raju, M. R., Robertson, J. B., 704
Carpenter, S. G., Raju, M. R. 720
Casteneda-Zuniga, W. R., Amplatz, K., Edwards, J. E., 633
Cattell, W. R., Cummack, Barbara, Jewell, Sandra E., Kelsey Fry, I., Webb, Judith A. W., 106
Chaffey, J. T., Bloomer, W. D., Dritschilo, A., Marck, A., 370
Chalmers, A. H., Armstrong, P., Green, G., Irving, J. D., 333
Chatterton, B. E., 981
Chisholm, G. D., Ruutu, M., Sherwood, T., 99
Cho, K. J., Oronzi, V. R., Raja Rao, A. K., Walter, J. F., 260
Christensen, E. E., Dietz, G. W., 830
Chudáček, Z., 855
Chu, J. M. G., Cosgrove, D. O., Husband, J. E., McCready, V. R., 728
Chu, J. M. G., Garvie, N. W., McCready, V. R., Nuttall, J., 547
Churchill-Davidson, I. F. J., Bleehen, N. M., Brindle, J., Bullimore, J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Clare, M. G., Joslin, C. A., 926
Clarke, M. B., Barrett, J. J., Howard, E. R., Jenner, R. E., 858, 862
Clark, R. A., Grech, P., Robinson, A., Townsend, R. H., 432
Clark, W. M., Haunch, T., Kelvin, F. M., Thompson, W. M., 826
Clavel, M., Sacher, M., Tenner, M., 736
Cochrane Shanks, S., 837
Cole, S. M., Henson, P. W., 262
Cole, T. P., Girdwood, T. G., Salter, R. H., Scott-Harden, W. G., 257
Collins, J. D., Furmanski, S., Poe, N., Steckel, R. J., 35
Collins, R. E. C., Field, S., Ward, A., 1012
Copland, W. A., McDicken, W. N., Wild, S. R., 824
Cosgrove, D. O., Chu, J. M. G., Husband, J. E., McCready, V. R., 728
Cotton, P. B., Johnson, A. L., Reuben, A., 956
Coupland, R. E., Mansfield, P., Morris, P. G., Pykett, I. L., 921
Cox, R. A., Amols, H. I., Bain, E., Carpenter, S. G., Robertson, J. B., Raju, M. R., 712
Cox, R. A., Bain, E., Carpenter, S. G., Raju, M. R., Robertson, J. B., 704
Cox, P. H., Tjen, H. S. L. M., van der Pompe, W. B., 396
Cremin, B. J., Fisher, R. M., Hochschild, T. J., 584
Cremin, B. J., Funston, M. R., 665
Cremin, B. J., Witcombe, J. B., 347
Croft, D. N. (British Nuclear Medicine Society), 59
Crooks, H. E., Ardran, G. M., 29
Crooks, H. E., Ardran, G. M., Birch, R., 867.
Cummack, Barbara, Cattell, W. R., Jewell, Sandra E., Kelsey Fry, I., Webb, Judith A. W., 106

Dale, R. G., 613
Dalla Palma, L., Bazzocchi, M., di Pietrantonio, M., 484
Dalrymple, R., Fataar, S., Schulman, A., Tidbury, I., 420
Dalrymple, R. B., Schulman, A., 494
Darlington, L. Gail, Gompels, B. M., 1018
Das, K. R., Santhamma, A. V., 507
Davidson, J., Bleehen, N. M., Brindle, J. Bullimore, J., Churchill-Davidson, I. F. J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Davis, J. B., Dovey, P., Thomson, D. M., 545
Davis, R., Tonge, K. A., 731
Dawson, J. L., Laws, J. W., Mackenzie, R. L., Tubbs, H. R., Williams, R., 953
de Dombal, F. T., Bresnihan, E., Fakes, S., Horrocks, J., Parkin, G. J. S., Smith, S. E. W., 528
de Lacey, G., 691
Denekamp, Juliana, 636
Denekamp, Juliana, Flockhart, I. R., McNally, N. J., Sheldon, P. W., 317
Denekamp, Juliana, Hill, Sally A., 997
Denekamp, Juliana, McNally, N. J., 747
Denekamp, Juliana, Stewart, F. A., 307
de Santos, L. A., Jing, B.-S., 682
de Silva, R. T. D., Bunton, R. W., Grennan, D. M., Palmer, D. G., 963
Dewbury, K. C., Guyer, P. B., 574
Dicello, J. F., Amols, H. I., Graves, R. U., Howard, J., Koehler, A. M., Lyman, J. T., Raju, M. R., Smathers, J. B., 699
Dick, A. P., Berridge, F. R., Freeman, A. H., Gleeson, J. A., Zeegen, R., 782
Dick, R., Barnes, N. R., Boulis, Z. F., 851
Dietz, G. W., Christensen, E. E., 830
di Pietrantonio, M., Bazzocchi, M., Dalla Palma, M., 484
Dische, S., 888
Dische, S., Anderson, P., Bleehen, N., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Dische, S., Cade, I. S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D., Saunders, M. I., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
Dixon-Brown, A., Ardran, G. M., Fursdon, P. S., 210
Doherty, C. C., Douglas, J. F., McGeown, Mary G., 802
Doran, J., Bell, G. D., McAllister, J., McMullin, J., Monks, A., Oliver, J., Richens, A., 251
Douglas, J. F., Doherty, C. C., McGeown, Mary G., 802
Dovey, P., Davis, J. B., Thomson, D. M., 545
Dritschilo, A., Bloomer, W. D., Chaffey, J. T., Marck, A., 370
Duncan, W., 943

Edelstein, T., Joel-Cohen, S. J., Schoenfeld, A., 742
Edwards, J. E., Amplatz, K., Casteneda-Zuniga, W. R., 633
Edwards, M., Abadir, R., 653
Eisenberg, R. L., Hedgcock, M. W., 916
Eisenberg, R., Russell, E., Spindola-Franco, H., 463
Ellis, R. E., Nordin, B. E. C., Tothill, P., Veall, N., 395

Evans, A. N. W., Amin, P. H., 539
Evans, R. A., McDonnell, G. D., Shieb, M., 428

Faarup, P., Hegedüs, V., Lønholdt, C., Nørgaard, T., 793
Fahrenkrug, A., Hansen, Elsemarie Berg, Praestholm, J., 321
Fakes, S., Bresnihan, E., de Dombal, F. T., Horrocks, J., Parkin, G. J. S., Smith, S. E. W., 528
Farmer, F. T., Harrison, R. M., 448
Farrant, P., Meire, H. B., 387, 628, 968
Fataar, S., Dalrymple, R., Schulman, A., Tidbury, I., 420
Fataar, S., Schulman, A., Tidbury, I., 389
Faw, F., 557
Fawcitt, R. A., Forbes, W. St. D., Braganza, J.M., Howat. H. T., Isherwood, I., 1
Fayadah, M., Bell, G. D., Frank, J., Kelsey Fry, I., McMullin, J., 111
Fayadah, M., Bell, G.D., Frank, J., Kelsey Fry, I., Smith, P.L.C. 191
Feder, B. H., George III, F. W., Neblett, D., Nisar Syed, A. M., 814
Ferrari, Liliana Recanatini, Rossi, G., Zanetti, E., 161
Field, S. B., Ahier, R.G., Law, Marilyn, P., 132
Field, S. B., Hume, Susan P., 302
Field, S. B., Law, Marilyn, P., 221
Field, S., Collins, R. E. C., Ward, A., 1012
Fisch, A. E., Brodey, P. A., Mall, J. C., Salman, B. J., 688
Fischman, E., 475
Fisher, R. M., Cremin, B. J., Hochschild, T. J., 584
Flockhart, I. R., Denekemp, Juliana, McNally, N. J., Sheldon, P. W., 317
Flower, C. D. R., 223
Flower, C. D. R., Kitchener, P. G., 543
Fonck, K., Konings, A. W. T., 832
Foote, G. A., Wilson, A. J., Stewart, J. H., 351
Forbes, W. St. C., Fawcitt, R. A., Braganza, J. J Howat, H. T., Isherwood, I., 1
Fowler, J. F., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Francis, P., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Francois, P., Al Jarallah, M. I., Archer-Hall, J. A., 392, 821
Frank, J., Bell, G. D., Fayadah, M., Kelsey Fry, I., McMullin, J., 111
Frank, J., Bell, G. D., Fayadah, M., Kelsey Fry I., Smith, P. L. C., 191
Freeman, A. H., Berridge, F. R., Dick, A. P., Gleeson, J. A., Zeegen, R., 782
Frühling, J., 395
Fuchs, W. A., 481
Funston, M. R., Cremin, B. J., 665
Furmanski, S., Collins, J. D., Poe, N., Stecke, R. J., 35
Fursdon, P. S., Ardran, G. M., Brodribb, A. J. M. Gear, J. S. S., Nolan, D. J., 472
Fursdon, P. S., Ardran, G. M., Dixon-Brown, A., 210

Gajaraj, A., Nedungadi, T. M. B., Rajagopalan, K. R., Rethinasabapathi, C., 140
Garrett, J. A., Poole, A., 733
Garvie, N. W., Ackery, D. M., Harrison, G. S. M. 825
Garvie, N. W., Chu, J. M. G., McCready, V. R., Nuttall, J., 547
Gear, J. S. S., Ardran, G. M., Brodribb, A. J. M., Fursdon, P. S., Nolan, D. J., 472
George III, F. W., Feder, B. H., Nelett, D., Nisar Syed, A. M., 814
Gifford, D., 557
Girdwood, T. G., 556
Girdwood, T. G., Cole, T. P., Salter, R. H., Scott-Harden, W. G., 257
Glasgow, J. F. T., Thomas, P. S., 93
Gleeson, J. A., Berridge, F. R., Dick, A. P., Freeman, A. H., Zeegen, R., 782
Glinska, H., Szymczyk, W., 750
Goldblatt, M., Schulman, A., Shaff, M. I., 396
Goldman, M., 473
Gompels, B. M., 748
Gompels, B. M., Darlington, L. Gail, 1018
Goulding, K. P., Walton, F. W., 1003
Grainger, R. G., 396
Graves, R. U., Amols, H. I., Dicello, J. F., Howard, J., Koehler, A. M., Lyman, J. T., Raju, M. R., Smathers, J. B., 699
Grdina, D. J., Linde, S., Mason, K., 291
Grech, P., Clark, R. A., Robinson, A., Townsend R. H., 432
Green, G., Armstrong, P., Chalmers, A. H., Irving, J. D., 333
Greening, J. R., 1026
Greenwell, F. P., 929
Gregory, N. L., 473
Grennan, D. M., Bunton, R. W., Palmer, D. G., de Silva, R. T. D., 963
Griffiths, G., Katzberg, R. W., 913
Grunebaum, M., Reider-Grosswasser, I., 671
Guelette, J., Guichard, M., Laublin, G., Malaise, E. P., Wambersie, A., 550
Guichard, M., Guelette, J., Laublin, G., Malaise, E. P., Wambersie, A., 550
Gupta, A., 589
Guyer, P. B., Dewsbury, K. C., 574

Hackford, A. W., Josel, M., Mann, N., Moskowitz, H., Polivy, C., 541
Hadden, R. C. M., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Haendle, J., Pfeifer, M., 139
Hale, T. I., Jucker, A., 139
Halnan, K. E., 395
Halnan, K. E., Cade, I. S., Dische, S., McEwan, J. B., Perrins, D. J. D., Saunders, M. I., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
Hammond, B. J., Wootton, R., 265
Hansen, Elsemarie Berg, Fahrenkrug, A., Praestholm, J., 321
Harbottle, Elizabeth, A., 556
Harkányi, Z., Szollár, J., Vigvári, Z., 46
Harris, J. W., Shrieve, D. C., 1024
Harrison, G. H., McCready, W. A., Robinson, J. E., Samuras, G. M., 532
Harrison, G. S. M., Ackery, D. M., Garvie, N. W., 825
Harrison, R. M., Farmer, F. T., 448

INDEX TO AUTHORS—*continued*

Hately, W., Cargill, A., 910
Hauch, T., Clarke, W. M., Kelvin, F. M., Thompson, W. M., 826
Haybittle, J. L., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Hedgcock, M. W., Eisenberg, R. L., 916
Hegedüs, V., Faarup, P., Lønholdt, C., Nørgaard, T., 793
Hendry, J. H., 808
Hendry, J. H., Sutton, M. L., 927
Hendry, J. H., Williams., P. C., 220
Henry, W. H., 141
Henson, P. W., Cole, S. M., 262
Hering, E. R., Le Roux, P. L. M., Sealy, R., 392
Herman, M. W., 225
Herzig, M., McLachlan, M. S. F., 503
Hill, C. K., Baarli, J., Bianchi, Marilena, Sullivan, A. H., 127
Hill, R. P., Bush, R. S., Siemann, D. W., 992
Hill, Sally A., Denekamp, Juliana, 997
Hilson, A. J. W., Bingham, J. B., Maisey, M. N., 342
Hinshaw, W. S., Andrew, E. R., Bottomley, P. A., Holland, G. N., Moore, W. S., Worthington, B. S., 273
Hirschmann, P. N., 837
Hobday, Pauline, Parker, R. P., 925
Hochhäuser, E., Balk, O. A., 460
Hochschild, T. J., Cremin, B. J., Fisher, R. M., 584
Hoiseth, A., Lowe, P., Nordshus, T., 1014
Holland, G. N., Andrew, E. R., Bottomley, P. A., Hinshaw, W. S., Moore, W. S., Worthington, B. S., 273
Hornsey, Shirley, 905
Hornsey, Shirley, White, Ann, 515
Horrocks, J., Bresnihan, E., de Dombal, F. T., Fakes, S., Parkin, G. J. S., Smith, S. E. W., 528
Horton, P. W., Adams, F. G., 281
Howard, E. R., Barrett, J. J., Clarke, M. B., Jenner, R. E., 858, 862
Howard, J., Amols, H. I., Dicello, J. F., Graves, R. U., Koehler, A. M., Lyman, J. T., Raju, M. R., Smathers, J. B., 699
Howard, N., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Howat, H. T., Braganza, J. M., Fawcitt, R. A., Forbes, W. St. C., Isherwood, J. M., 1
Hudson, F. R., Mott, G. T., Thompson, D. M., Wylie, B. A., 58
Huisman, P. A., Karzmark, C. J., Rust, D. C., 1026
Hume, Susan P., Field, S. B., 302
Husband, J. E., Chu, J. M. G., Cosgrove, D. O., McCready, V. R., 728
Husband, Janet, Saxton, H. M., 11
Hynes, M. A., Lloyd, D. C., Purrott, R. J., Reading, D. H., Spinks, W. S., Stephenson, B. D., 41

Ingvar, D. H., 657
Irving, J. D., Armstrong, P., Chalmers, A. H., Green, G., 333
Isherwood, I., Braganza, J. M., Fawcitt, R. A., Forbes, W. St. C., Howat, H. T., 1
Itai, Y., Shimazu, H., 469
Itti, R., Brochier, M., Pellois, A., Planiol, T. 443
Iyer, P. S., 471

Jackson, G., Jewitt, D., Kyriakidis, M., 799
James, K. W., Ngan, H., 788
James, W. B., 1020
Jenner, R. E., Barrett, J. J., Clarke, M. B., Howard, E. R., 858, 862
Jewell, Sandra, E., Cattell, W.R., Cummack, Barbara, Kelsey Fry, I., Webb, Judith A. W., 106
Jewitt, D., Jackson, G., Kyriakidis, M., 799
Jing, B–S, de Santos, L. A., 682
Joel-Cohen, S. J., Edelstein, T., Schoenfeld, A., 742
Johnson, A. J., Burrows, E. H., 196
Johnson, A. L., Cotton, P. B., Reuben, A., 956
Jones, Bronwyn, 466
Jones, D. E. A., 141
Josel, M., Hackford, A. W., Mann, N., Moskowitz., H., Polivy, C., 541
Joslin, C. A., Clare, M. G., 926
Jucker, A., Hale, T. I., 139
Julian, W. L., Bryant, T. H. E., 974
Junor, B. J. R., Smith, F. W., 741

Karcher, K. H., Anderson, P., Bleehen, N., Dische, S., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Karzmark, C. J., Huisman, P. A., Rust, D. C., 1026
Katzberg, R. W., Griffiths, G., 913
Keeling, D. H., Bowring, C. S., 836
Kelsey Fry, I., Bell, G. D., Fayadah, M., Frank, J., McMullin, J., 111
Kelsey Fry, I., Bell, G. D., Fayadah, M., Frank, J., Smith, P. L. C., 191
Kelsey Fry, I., Cattell, W. R., Cummack, Barbara, Jewell, Sandra, E., Webb, Judith A. W., 106
Kelvin, F. M., Clark, W. M., Hauch, T., Thompson, W. M., 826
Kendall, B. E., Kingsley, D., 171
Kendall, B. E., Radue, E. W., 563
Kendall, B. E., Tatler, G. L. V., 81
Keyes, W. I., Mallard, J. R., 61
Khan, R. A., Best, J. K., Lavender, J. P., 51
Kim, C. Y., Bahk, Y. W., 847
Kim, S. C., Yau, T. M., 551
Kingsley, D., Kendall, B. E., 171
Kitchener, P. G., Flower, C. D. R., 543
Klein, D. L., 548
Koehler, A. M., Amols, H. I., Dicello, J. F., Graves, R. U., Howard, J., Lyman, J. T., Raju, M. R., Smathers, J. B., 699
Kogelnik, H. D., Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Phillips, T. L., Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Konings, A. W. T., Fonck, K., 832
Konstantoulas, M., 56
Kyriakidis, M., Jackson, G., Jewitt, D., 799

Lakshmanan, A. V., Mallard, J., Sharp, P., 986
Lansley, I. F., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lindup, R., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Laublin, G., Guichard, M., Guelette, J., Malaise, E. P., Wambersie, A., 550

INDEX TO VOLUME 51

Lavelle, M. I., Owens, J. P., Rawlins, M. D., 653
Lavender, J. P., Best, J. K., Khan, R. A., 51
Law, Marilyn P., Ahier, R. G., Field, S. B., 132
Law, Marilyn P., Field, S. B., 221
Law, Marilyn P., Thomlinson, R. H., 895
Laws, J. W., Dawson, J. L., Mackenzie, R. L., Tubbs, H. R., Williams, R., 953
Lawson, R. S., O'Reilly, P. H., Shields, R. A., Testa, H. J., 223
Lehnert, Shirley, 923
Le Roux, P. L. M., Hering, E. R., Sealy, R., 392
Levick, R. K., Steiner, G. M., 20
Levin, W., Wasserman, H. J., 213
Linde, S., Grdina, D. J., Mason, K., 291
Lindup, R., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Phillips, D. L., Skeggs, D., Wiernik, G., 241
Lloyd, D. C., Hynes, M. A., Purrott, R. J., Reading, D. H., Spinks, W. S., Stephenson, B. D., 41
Lønholdt, C., Farrup, P., Hegedüs, V., Nørgaard, T., 793
Lowe, D., 60
Lowe, P., Hoiseth, A., Nordshus, T., 1014
Luppi, A., Meurman, K. O. A., Turunen, M. J., 919
Lyman, J. T., Amols, H. I., Dicello, J. F., Graves, R. U., Howard, J., Koehler, A. M., Raju, M. R., Smathers, J. B., 699

McAllister, J., Bell, G. D., Doran, J., McMullin, J., Monks, A., Oliver, J., Richens, A., 251
McAllister, J., Bell, G. D., McMullin, J., Oliver, J., 17
McCready, V. R., Chu, J. M. G., Cosgrove, D. O., Husband, J. E., 728
McCready, V. R., Chu, J. M. G., Garvie, N. W., Nuttall, J., 547
McCready, W. A., Harrison, G. H., Robinson, J. E., Samuras, G. M., 532
McCulloch, J. A., Waddell, G., 498
McDicken, W. N., Copland, W. A., Wild, S. R., 824
McDonald, J. M., Zeitz, L., 637
McDonnell, G. D., Evans, R. A., Schieb, M., 428
MacErlean, D. P., Martin, E. A., Shanik, D. G., 414
McEwan, J. B., Cade, I. S., Dische, S., Halnan, K. E., Perrins, D. J. D., Saunders, M. I., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
McGeown, Mary G., Doherty, C. C., Douglas, J. F., 802
Mackenzie, R. L., Dawson, J. L., Laws, J. W., Tubbs, H. R., Williams, R., 953
McLachlan, M. S. F., Herzig, M., 503
McMullin, J., Bell, G. D., Doran, J., McAllister, J., Monks, A., Oliver, J., Richens, A., 251
McMullin, J., Bell, G. D., Fayadah, M., Frank, J., Kelsey Fry, I., 111
McMullin, J., Bell, G. D., McAllister, J., Oliver, J., 17
McNally, N. J., Denekamp, Juliana, 747
McNally, N. J., Denekamp, Juliana, Flockhart, I. R., Sheldon, P. W., 317
Machell, R. J., Calne, R. Y., 631
Macpherson, P., 5
Maisey, M. N., Bingham, J. B., 599
Maisey, M. N., Bingham, J. B., Hilson, A. J. W., 342
Malaise, E. P., Guichard, M., Guelette, J. Laublin, G., Wambersie, A., 550
Mall, J. C., Brodey, P. A., Fisch, A. E., Salman, B. J., 688
Mallard, J. R., Keyes, W. I., 61
Mallard, J., Lakshmanan, A. V., Sharp, P., 986
Malone, J. F., 553
Malone, J. F., Moriarty, M., Mothersill, Carmel, O'Connor, M. K., 474
Malone, J. F., O'Connor, M. K., 454
Mann, N., Hackford, A. W., Josel, M., Moskowitz, H., Polivy, C., 541
Mansfield, P., Coupland, R. E., Morris, P. G., Pykett, I. L., 921
Marck, A., Bloomer, W. D., Chaffey, J. T., Dritschilo, A., 370
Marr, S. P., 225
Martin, E. A., MacErlean, D. P., Shanik, D. G., 420
Mason, K., Grdina, D. J., Linde, S., 291
Maze, M., Agnew, J. E., 206
Meire, H. B., Farrant, P., 387, 628, 968
Meredith, H. C., O'Brien, P. H., Schabel, S. I., Vujic, I., 1011
Meredith, H. C., Valicenti, J. F., 218
Meurman, K. O. A., Luppi, A., Turunen, M. J., 919
Mijnheer, B. J., Broerse, J. J., Zoetelief, J., 122
Mole, R. H., 401
Møller, Inge, Petersen, Jørgen, 915
Monks, A., Bell, G. D., Doran, J., McAllister, J., McMullin, J., Oliver, J., Richens, A., 251
Moore, W. S., Andrew, E. R., Bottomley, P. A., Hinshaw, W. S., Holland, G. N., Worthington, B. S., 273
Moriarty, M., Malone, J. F., Mothersill, Carmel, O'Connor, M. K., 474
Morris, P. G., Coupland, R. E., Mansfield, P., Pykett, I. L., 921
Moskowitz, H., Hackford, A. W., Josel, M., Mann, N., Polivy, C., 541
Mothersill, Carmel, Malone, J. F., Moriarty, M., O'Connor, M. K., 474
Mott, G. T., Hudson, F. R., Thompson, D. M., Wylie, B. A., 58
Murnaghan, D. J., 748

Nagarajan, P. S., Bhatia, D. P., 223
Nagaratnam, A., Reddy, A. R., 931
Neblett, D., Feder, B. H., George III, F. W., Nisar Syed, A. M., 814
Nedungadi, T. M. B., Gajaraj, A., Rajagopalan, K. R., Rethinasabapathi, C., 140
Newlands, E. S., 756
Ngan, H., James, K. W., 788
Nikapota, V. L. B., Wray, M. I., 1016
Nisar Syed, A. M., Feder, B. H., George III, F. W., Neblett, D., 814
Nolan, D. J., Ardran, G. M., Brodribb, A. J. M., Fursdon, P. S., Gear, J. S. S., 472
Nordin, B. E. C., Ellis, R. E., Tothill, P., Veall, N., 395
Nordshus, T., Hoiseth, A., Lowe, P., 1014
Nørgaard, T., Farrup, P., Hegedüs, V., Lønholdt, C., 793
Nuttall, J., Chu, J. M. G., Garvie, N. W., McCready, V. R., 547

O'Brien, P. H., Meredith, H. C., Schabel, S. I., Vujic, I., 1011
O'Connell, D. J., Thompson, A. J., 203
O'Connor, M. K., Malone, J. F., 454

INDEX TO AUTHORS—continued

O'Connor, M. K., Malone, J. F., Moriarty, M., Mothersill, Carmel, 474
Oliver, J., Bell, G. D., Doran, J., McAllister, J., McMullin, J., Monks, A., Richens, A., 251
Oliver, J., Bell, G. D., McAlister, J., McMullin, J., 17
O'Reilly, P. H., Lawson, R. S., Shields, R. A., Testa, H. J., 223
Oronzi, V. R., Cho, K. J., Raja Rao, A. K., Walter, J. F., 260
Owens, J. P., Lavelle, M. I., Rawlins, M. D., 653

Page, B. C., Bewley, D. K., 375
Palmer, D. G., Bunton, R. W., Grennan, D. M., de Silva, R. T. D., 963
Panzer, W., Seelentag, W. W., 529
Park, W. M., Cannell, L. B., Timothy, A. R., Tucker, Audrey, K., 328
Parker, R. P., Hobday, Pauline, 925
Parkin, G. J. S., Bresnihan, E., de Dombal, F. T., Fakes, S., Horrocks, J., Smith, S. E. W., 528
Pellois, A., Brochier, M., Itti, R., Planiol, T., 443
Perrins, D. J. D., Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Saunders, M. I., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
Petersen, Jørgen, Møller, Inge, 915
Pfeifer, M., Haendle, J., 139
Phelps, P. D., Ashley, A. J., 437
Phillips, D. L., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Skeggs, D., Wiernik, G., 241
Phillips, T. L., Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Kogelnik, H., D. Saunders, M. I., Urtasun, R. C., Wasserman, T. H., 1023
Planiol, T., Brochier, M., Itti, [R., Pellois, A., 443
Poe, N., Collins, J. D., Furmanski, S., Steckel, R. J., 35
Polivy, C., Hackford, A. W., Josel, M., Mann, N., Moskowitz, H., 541
Praestholm, J., Fahrenkrug, A., Hansen, Elsemarie Berg, 321
Preuss, L. E., Bolin, F. P., 750
Propp, H., 930
Prosser, J. S., White, C. M., 654
Puijlaert, C. B. A. J., 930
Pullan, B. R., Roberts, E. Trudie, 24
Purrott, R. J., Hynes, M. A., Lloyd, D. C., Reading, D. H., Spinks, W. S., Stephenson, B. D., 41
Pykett, I. L., Coupland, R. E., Mansfield, P., Morris, P. G., 921

Radue, E. W., Kendall, B. E., 563
Rajagopalan, K. R., Gajaraj, A., Nedungadi, T. M. B., Rethinasabapathi, C., 140
Raja Rao, A. K., Cho, K. J., Oronzi, V. R., Walter, J. F., 260
Raju, M. R., Amols, H. I., Bain, E., Carpenter, S. G., Cox, R. A., Robertson, J. B., 712
Raju, M. R., Amols, H. I., Dicello, J. F., Graves, R., Howard, J., Koehler, A. M., Lyman, J. T., Smathers, J. B., 699
Raju, M. R., Bain, E., Carpenter, S. G., Cox, R. A., Robertson, J. B., 704
Raju, M. R., Carpenter, S. G., 720
Rawlins, M. D., Lavelle, M. I., Owens, J. P., 653
Reading, D. H., Hynes, M. A., Lloyd, D. C., Purrott, R. J., Spinks, W. S., Stephenson, B. D., 41
Recanatini, Liliana Ferrari, Rossi, G., Zanetti, E., 161
Reddy, A. R., Nagaratnam, A., 931
Redpath, J. L., 524
Reider-Grosswasser, I., Grunebaum, M., 671
Rethinasabapathi, C., Gajaraj, A., Nedungadi, T. M. B., Rajagopalan, K. R., 140
Reuben, A., Cotton, P. B., Johnson, A. L., 956
Richens, A., Bell, G. D., Doran, J., McAllister, J., McMullin, J., Monks, A., Oliver, J., 251
Riordan, J. F., Banks, R. A., Rudolf, M., Saunders, K. B., 286
Roberts, E. Trudie, Pullan, B. R., 24
Robertson, J. B., Amols, H. I., Bain, E., Carpenter, S. G., Cox, R. A., Raju, M. R., 712
Robertson, J. B., Bain, E., Carpenter, S. G., Cox, R. A., Raju, M. R., 704
Robinson, A., Clark, R. A., Grech, P., Townsend, R. H., 432
Robinson, J. E., Harrison, G. H., McCready, W. A., Samuras, G. M., 532
Rofstad, E. K., Brustad, T., 381
Rossi, G., Ferrari, Liliana Recanatini, Zanetti, E., 161
Rudolf, M., Banks, R. A., Riordan, J. F., Saunders, K. B., 286
Russell, E., Eisenberg, R., Spindola-Franco, H., 463
Rust, D. C., Huisman, P. A., Karzmark, C. J., 1026
Ruutu, M., Chisholm, G. D., Sherwood, T., 99

Sacher, M., Clavel, M., Tenner, M., 736
Salman, B. J., Brodey, P. A., Fisch, A. E., Mall, J. C., 688
Salter, R. H., Cole, T. P., Girdwood, T. G., Scott-Harden, W. G., 257
Samuras, G. M., Harrison, G. H., McCready, W. A., Robinson, J. E., 532
Santhamma, A. V., Das, K. R., 507
Saunders, K. B., Banks, R. A., Riordan, J. F., Rudolf, M., 286
Saunders, M. I., Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Urtasun, R. C., Wasserman, T. H., 1023
Saunders, M. I., Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D., Sutherland, I., Watson, E. R., Wiernik, G., 876, 879
Saxton, H. M., Husband, Janet, 11
Schabel, S. I., Meredith, H. C., O'Brien, P. H., Vujic, I., 1011
Schieb, M., Evans, R. A., McDonnell, G. D., 428
Schoenfeld, A., Edelstein, T., Joel-Cohen, S. J., 742
Schulman, A., Dalrymple, R. B., 494
Schulman, A., Dalrymple, R., Fataar, S., Tidbury, I., 420
Schulman, A., Fataar, S., Tidbury, I., 389
Schulman, A., Goldblatt, M., Shaff, M. I., 396
Scott-Harden, W. G., Cole, T. P., Girdwood, T. G., Salter, R. H., 257
Sealy, R., Hering, E. R., LeRoux, P. L. M., 392
Sear, R., 59
Seelentag, W. W., Panzer, W., 529
Shaff, M. I., Goldblatt, M., Schulman, A., 396
Shah, B. D., 1025
Shah, V., Singhal, N. C., Udawat, J. P., 608
Shanik, D. G., MacErlean, D. P., Martin, E. A., 414

INDEX TO VOLUME 51

Sharp, P., Lakshmanan, A. V., Mallard ,J., 986
Sheldon, P. W., Denekamp, Juliana, Flockhart, I. R., McNally, N. J., 317
Sherwood, T., Chisholm, G. D., Ruutu, M., 99
Shields, R. A., Lawson, R. S., O'Reilly, P. H., Testa, H. J., 223
Shimazu, H., Itai, Y., 469
Shirley, I., Vicary, F. R., 596
Shrieve, D. C., Harris, J. W., 1024
Siemann, D. W., Bush, R. S., Hill, R. P., 992
Singhal, N. C., Shah, V., Udawat, J. P., 608
Singh, K., 357
Skeggs, D., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Wiernik, G., 241
Smathers, J. B., Amols, H. I., Dicello, J. F., Graves, R. U., Howard, J., Koehler, A. M., Lyman, J. T., Raju, M. R., 699
Smidt, K. P., Andrews, J. T., 50
Smith, C. B., 931
Smith, F. W., Junor, B. J. R., 741
Smith, P. L. C., Bell, G. D., Fayadah, M., Frank, J., Kelsey Fry, I., 191
Smith, S. E. W., Bresnihan, E., de Dombal, F. T., Fakes, S., Horrocks, J., Parkin, G. J. S., 528
Smythe, G. E., 929
Spiers, F. W., Beddoe, A. H., Whitwell, Joan R., 622
Spindola-Franco, H., Eisenberg, R., Russell, E., 463
Spinks, W. S., Hynes, M. A., Lloyd, D. C., Purrot, R. J., Reading, D. H., Stephenson, B. D., 41
Steckel, R. J., Collins, J. D., Furmanski, S., Poe, N., 35
Steiner, G. M., 406
Steiner, G. M., Levick, R. K., 20
Stephenson, B. D., Hynes, M. A., Lloyd, D. C., Purrot, R. J., Reading, D. H., Spinks, W. S., 41
Stewart, F. A., Denekamp, Juliana, 307
Stewart, J. H., Foote, G. A., Wilson, A. J., 351
Stratford, I. J., Adams, G. E., 745
Sullivan, A. H., Baarli, J., Bianchi, Marilena, Hill, C. K., 127
Sutherland, G. R., 116
Sutherland, I., Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D., Saunders, M. I., Watson, E. R., Wiernik, G., 876, 879
Sutton, M. L., Hendry, J. H., 927
Svoboda, V. H. J., 363
Syed, I. B., 475
Szollár, J., Harkányi, Z., Vigvári, Z., 46
Szymczyk, W., Glinska, H., 750

Tatler, G. L. V., Kendall, B. E., 81
Tenner, M., Clavel, M., Sacher, M., 736
Testa, H. J., Lawson, R. S., O'Reilly, P. H., Shields, R. A., 223
Thomas, P. S., Glasgow, J. F. T., 93
Thomlinson, R. H., Law, Marilyn P., 895
Thompson, A. J., O'Connell, D. J., 203
Thompson, D. M., Hudson, F. R., Mott, G. T., Wylie, B. A., 58
Thompson, W. M., Clark, W. M., Hauch, T., Kelvin, F. M., 826
Thomson, D. M., Dovey, P., Davis, J. B., 545
Tidbury, I., Dalrymple, R., Fataar, S., Schulman, A., 420
Tidbury, I., Fataar, S., Schulman, A., 389
Timothy, A. R., Cannell, L. B., Park, W. M., Tucker, Audrey K., 328
Tjen, H. S. L. M., Cox, P. H., van der Pompe, W. B., 396
Tonge, K. A., Davis, R., 731
Tothill, P., Ellis, R. E., Nordin, B. E. C., Veall, N., 395
Townsend, R. H., Clark, R. A., Grech, P., Robinson, A., 432
Tubbs, H. R., Dawson, J. L., Laws, J. W., Mackenzie, R. L., Williams, R., 953
Tucker, Audrey K., Cannell, L. B., Park, W. M., Timothy, A. R., 328
Turunen, M. J., Luppi, A., Meurman, K. O. A., 919

Udawat, J. P., Shah, V., Singhal, N. C., 608
Urtasun, R. C., Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Wasserman, T. H., 1023

Valicenti, J. F., Meredith, H. C., 218
van der Pompe, W. B., Cox, P. H., Tjen, H. S. L. M., 396
Vauramo, E., Virjo, A., 931
Veall, N., Ellis, R. E., Nordin, B. E. C., Tothill, P., 395
Vicary, F. R., Shirley, I., 596
Vigvári, Z., Harkányi, Z., Szollár, J., 46
Virjo, A., Vauramo, E., 931
Vujic, I., Meredith, H. C., O'Brien, P. H., Schabel, S. I., 1011

Waddell, G., McCulloch, J. A., 498
Waggett, D. J., Wilson, B. C., 1004
Walker, T. M., Ashcroft, M. T., 338
Walter, J. F., Cho, K. J., Oronzi, V. R., Raja Rao, A. K., 260
Walton, F. W., Goulding, K. P., 1003
Wambersie, A., Guichard, M., Guelette, J., Laublin, G., Malaise, E. P., 550
Ward, A., Collins, R. E. C., Field, S., 1012
Warrick, C. K., Carmichael, J. H. E., 843
Wasserman, H. J., Levin, W., 213
Wasserman, T. H., Anderson, P., Bleehen, N., Dische, S., Karcher, K. H., Kogelnik, H. D., Phillips, T. L., Saunders, M. I., Urtasun, R. C., 1023
Waters, G., 1026
Watson, E. R., Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D., Saunders, M. I., Sutherland, I., Wiernik, G., 876, 879
Watson, J. V., 534, 557
Webb, Judith, A. W., Cattell, W. R., Cummack, Barbara, Jewell, Sandra E., Kelsey Fry, I., 106
White, Ann, Hornsey, Shirley, 515
White, C. M., Prosser, J. S., 654
White, D. R., 397
Whitwell, Joan R., Beddoe, A. H., Spiers, F. W., 622
Wiernik, G., Bleehen, N. M., Brindle, J., Bullimore, J., Churchill-Davidson, I. F. J., Davidson, J., Fowler, J. F., Francis, P., Hadden, R. C. M., Haybittle, J. L., Howard, N., Lansley, I. F., Lindup, R., Phillips, D. L., Skeggs, D., 241
Wiernik, G., Cade, I. S., Dische, S., Halnan, K. E., McEwan, J. B., Perrins, D. J. D.,

INDEX TO AUTHORS—continued

Saunders, M. I., Sutherland, I., Watson, E. R., 876, 879
Wild, S. R., Copland, W. A., McDicken, W. N., 824
Willets, R. J., 929
Williams, P. C., Hendry, J. H., 220
Williams, R., Dawson, J. L., Laws, J. W., Mackenzie, R. L., Williams, R., 953
Wilson, A. J., Foote, G. A., Stewart, J. H., 351
Wilson, B. C., Waggett, D. J., 1004
Windeyer, Sir Brian, 875
Witcombe, J. B., 579
Witcombe, J. B., Cremin, B. J., 347
Wootton, R., Hammond, B. J., 265
Worthington, B. S., Andrew, E. R., Bottomley, P. A., Hinshaw, W. S., Holland, G. N., Moore, W. S., 273
Wray, M. I., Nikapota, V. L. B., 1016
Wylie, B. A., Hudson, F. R., Mott, G. T., Thompson, D. M., 58

Yau, T. M., Kim, S. C., 551

Zanetti, E., Ferrari, Liliana Recanatini, Rossi, G., 161
Zeegen, R., Berridge, F. R., Dick, A. P., Freeman, A. H., Gleeson, J. A., 782
Zeitz, L., McDonald, J. M., 637
Zoetelief, J., Broerse, J. J., Mijnheer, B. J., 122

INDEX TO SUBJECTS

1978

RADIODIAGNOSIS

Bones and Joints

(excluding skull)

Bone mineral measurement using an EMI scanner and standard methods: a comparative study, 24
Osteonecrosis in Hodgkin's disease, 328
Needle aspiration/biopsy of the spine in suspected disc space infection, 333
The metacarpal index in Jamaican children and adults, 338
Tuberculous erosion of the sphenoid bone, 347
Transcatheter embolization of bone tumour arteriovenous malformations, 414
Metacarpal cortical area as an index of bone mass, 428
Lateral lumbar discography, 498
Essential osteolysis of carpal and tarsal bones (Case report), 539
The hip joint in Paget's disease (Paget's "coxopathy"), 574
The early development of the human skeleton: a radiographic study of fetuses impregnated with silver nitrate, 584
Metaphyseal multifocal osteosarcoma, 671
Radiographic findings of Ewing's sarcoma of the jaws, 682
Intra-osseous vascular malformation of the mandible (Case report), 738
Peri-articular calcification with fluid levels in secondary hyperparathyroidism (Case report), 741
Positioning errors in bone mineral measurement (Technical note), 821
A radiographically documented intra-uterine femoral fracture (Case report), 830
Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage, 851
Bilateral pigmented villonodular synovitis of the hip (Case report), 919
A giant retrofemoral Baker's cyst (Case report), 919
Lateral sublaxation of the atlas in rheumatoid arthritis, 963

Neuroradiology

(including skull)

Pseudo-occlusion of the internal and carotid artery, 5
Bone mineral measurement using an EMI scanner and standard methods: a comparative study, 24
Radiological findings in neurosarcoidosis, 81
The value of computerized axial tomography (CAT) in cranio-cerebral malformations, 171
Thecal deformity after lumbar myelography with iophendylate (Myodil) and meglumine iothalamate (Conray 280), 196
Protection of the eye during carotid angiography, 262
Late meningeal effects of myelographic contrast media with special reference to metrizamide, 321
Computed tomography in spontaneous intracerebral haematomas, 563
Functional landscapes in the brain studied with regional blood flow measurements. (MacKenzie Davidson Memorial Lecture 1977), 657
Structural changes of the intradural arteries following subarachnoid haemorrhage (Case report), 736
Orbitocranial asymetry, 771
Non-thrombotic occlusion of the cavernous carotid from subdural empyema (Case report), 913

Cardiovascular System

Left ventricular-right atrial communication with aneurysm of the membranous intraventricular septum, 463
Contrast media during coronary arteriography: electrocardiographic changes in the presence of normal coronary arteries, 799
Spasm of the superior mensenteric artery complicating methysergide maleate therapy (Case report), 1014

Respiratory Tract

Bone mineral measurement using an EMI scanner and standard methods: a comparative study, 24
Solitary neurofibroma of the trachea (Case report), 218
The lymphographic anatomy of chylothorax, 420
Limitations of fibre-optic bronchoscopy under fluoroscopy in the investigation of peripheral lung lesions, 432
Subpulmonary pneumothorax, 494
Pleural cyst of the mediastinum (Case report), 548
Post-thoracotomy lung herniation, 688
Miliary pulmonary infiltrates and penicillamine (Case report), 915

Digestive Tract

Pneumatosis coli in non-Hodgkin's lymphoma, 203
Endoscopic and radiological assessment of recurrent ulceration after peptic ulcer surgery, 257
The importance of the anomalous left gastric artery in the arteriography or gastric haemorrhage, 260
The misplaced caecum and the root of the mesentery, 406
Ceco-sigmoid vovlulus – a new entity? 466
Leiomyosarcoma of the oesophagus with dense calcification, 469
Colonic lavage prior to barium enema—a comparison of two techniques (Technical note), 528
Examination of small bowel by double contrast technique (Correspondence), 556
Pneumatosis intestinalis in children, 589
Anterior vascular indentation of the oesophagus (Case report), 633
Pseudopolyposis in Crohn's disease, 781
Diagnosis of an ileal duplication with sodium pertechnetate^{99} Tc^{m} (Case report), 825
Chronic oesophageal stricture due to moniliasis (Case report), 826
Inverted Meckel's diverticulum as a cause of anaemia and continuing blood loss (Case report), 829
Preparation of the colon prior to radiology—a comparison of the effectiveness of castor oil, Dulcodos and X-Prep liquid (Technical note), 910
Phaeochromocytoma diagnosed during barium meal, 918
The double contrast meal—new high density barium sulphate powders (Short communication), 1020

INDEX TO VOLUME 51

Liver and Biliary Tract, Spleen, Pancreas

Computed tomography in a pancreatic disease, 1
Urinary excretion and patterns of protein binding of iodipamide (Biligrafin forte), 11
A simple spectrophotometric method for measuring biliary ioglycamide (Biligram) concentration, 17
Ioglycamide (Biligram) studies in man—relation between plasma concentration and biliary excretion, 111
Ioglycamide (Biligram) studies in man. Radiological opacification of the bile duct. A comparison of a number of different methods, 191
Ioglycamide (Biligram) studies in man—plasma binding, renal and biliary excretion studies in jaundiced and anicteric patients, 251
Lymphographic opacification of liver and spleen (Case report), 389
Narrow-needle (Chiba) cholangiography (Correspondence), 396
Faster contrast-passage through a Chiba needle in percutaneous trans-hepatic cholangiography (Correspondence), 396
Abdominal contrast tomography in the evaluation of the gall-bladder and biliary tract (with emphasis upon jaundiced patients), 484
Complications of "Chiba" needle trans-hepatic cholangiography (Case report), 541
Solitary non-parasitic hepatic cyst presenting with jaundice (Case report), 631
The biliary excretion of the stereo-isomers of iocetamic acid (Cholebrin) (Correspondence), 653
The B-scan ultrasonic appearances of gas in the biliary tree, 728
Hepatic oil embolism following lymphography, 788
Visualization of the cystic artery after injection of Pancreozymin, 855.
Obstructive jaundice and portal vein calcification, 953
Is pancreatogram interpretation reliable?—a study of observer variation and error, 956
Obstructive jaundice caused by cavernous transformation of the portal vein (Case report), 1011
Iocarmide (Biligram) studies in man (Correspondence), 1025

Urinary Tract

Renal angiography problems in live kidney donors, 99
Curve stripping of the third phase of the renogram in essential hypertension (Correspondence), 140
Wide ureters, a dilemma in diagnosis (Correspondence), 223
The appearances of renal transplant lymphocoeles during dynamic renal scintigraphy, 342
Multicystic kidney—an example of bilateral involvement in an adult (Case report), 543
Renal involvement with non-Hodgkin's lymphoma: investigation of a recent case (Case report), 547
Renal tubular sludging of meglumine iodipamide (Biligrafin), 579
Intrarenal reflux-papillary morphology and pressure relationships in children's necropsy kidneys, 665
Volume changes in the rat renal cortex during urography, 793
Isotope renography and long-term follow-up of renal transplant patients, 802
Radiologic manifestations of epidemic haemorrhage fever with renal syndrome, 847

Haemopoietic, Lymphatic, Reticulo-endothelial System

Clinical radionuclide perfusion lymphangiography, 35
The lymphographic anatomy of the chylothorax, 420
Hepatic oil embolism following lymphography, 788

Reproductive System

Classification and radiographic features of uterine malformations: hysterosalpingographic study (Review article), 161
A radiographically documented intra-uterine femoral fracture (Case report), 830

Endocrine System

Phaeochromocytoma diagnosed during barium meal (Case report), 918

Ear, Nose, Throat, Mouth, Eyes

The contribution of echography in the diagnosis of proptosis, 116

Breast and Soft Tissues

A phantom designed to compare the quality of various mammographic images (Technical note), 731
Tuberculosis of the breast (Case report), 1012

Paediatrics

The "mandibular mantle"—a sign of rickets in very low birth weight infants, 93
Perinatal post-mortem radiography—experience with 2 500 cases, 351
The misplaced caecum and the root of the mesentery, 406
The early development of the human skeleton: a radiographic study of fetuses impregnated with silver nitrate, 584
Pneumatosis intestinalis in children, 589
Intrarenal reflux—papillary morphology and pressure relationships in children's necropsy kidneys, 665
Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage, 851

Contrast Media and Other Drugs

Urinary excretion and patterns of protein binding of iodipamide (Biligrafin forte), 11
A simple spectrophotometric method for measuring biliary ioglycamide (Biligram) concentration, 17
The effect of osmotic diuresis on urinary iodine concentration using contrast media of differing osmolality, 106
Ioglycamide (Biligram) studies in man—relation between plasma concentration and biliary excretion, 111
Ioglycamide (Biligram) studies in man. Radiological opacification of the bile duct. A comparison of a number of different methods, 191
Ioglycamide (Biligram) studies in man—plasma binding, renal and biliary excretion studies in jaundiced and anicteric patients, 251
Renal tubular sludging of meglumine iodipamide (Biligrafin), 579
The biliary excretion of the stereo-isomers of iocetamic acid (Cholebrin) (Correspondence), 653
Contrast media during coronary arteriography: electrocardiographic changes in the presence of normal coronary arteries, 799

Apparatus and Technical Aspects

A comparative survey of multi-directional tomographic units, 437

Positioning errors in bone mineral measurement (Technical note), 821

Constancy of radiation output during diagnostic X-ray exposures, 867

Design of tomographic equipment (Correspondence), 929

Reduction of X-ray tube output during life (Correspondence), 1026

COMPUTERIZED AXIAL TOMOGRAPHY

Head

The value of computerized axial tomography (CAT) in cranio-cerebral malformations, 171

Computed tomography in spontaneous intracerebral haematomas, 563

"Floppy" into "flippy"—or two for the price of one (Technical note), 822

Whole body

Computed tomography in pancreatic disease, 1

Bone mineral measurement using an EMI scanner and standard methods: a comparative study, 24

RADIOTHERAPY

Results and Clinical Aspects

An improved technique for interstitial radiotherapy of the tongue, 213

Sixth Interim Progress Report of The British Institute of Radiology fractionation study of 3F/week versus 5F/week in radiotherapy of the laryngopharynx, 241

Central airways obstruction in carcinoma of the bronchus treated by radiotherapy: a study of pulmonary function, 286

Two regimes with the same TDF but differing morbidity used in the treatment of stage III carcinoma of the cervix, 357

Further experience with radiotherapy by multiple daily sessions, 363

The complication probability factor: a method for selection of radiation treatment plans, 370

Response of aneurysmal bone cyst to low doses of cobalt 60 gamma radiation with prolonged treatment, 608

Time, dose and fractionation factors for six fractions per week (Correspondence), 748

Iridium-192 afterloaded implant in the retreatment of head and neck cancers, 814

Hyperbaric oxygen and radiotherapy. The Medical Research Council's Working Party, 875

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the bladder, 876

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix, 879

Hyperbaric oxygen: the Medical Research Council trials and their clinical significance, 888

The relationship between total dose, number of fractions and fraction size in the response of malignant melanoma in patients, 905

Current thoughts on fast neutron therapy (Mackenzie Davidson Memorial Lecture, November 17, 1977), 943

The neurotoxicity of misonidazole: pooling of data from five centres (Correspondence), 1023

Apparatus and Technical Aspects

An improved technique for interstitial radiotherapy of the tongue, 213

The RBE of megavoltage photon and electron beams (Short communication), 220

The complication probability factor: a method for selection of radiation treatment plans, 370

The determination of anatomical cross-sections using a radiotherapy simulator, 448

Tissue-air ratios for whole body irradiation with cobalt 60 gamma rays (Technical note), 460

Dosimetry of cathetron applicators in intracavitary therapy, 507

Implementation of the Philips treatment planning system for use in radiation teletherapy, 613

A lightweight breast applicator for setting up tangential fields (Correspondence), 653

Electronic dual timer for a teletherapy machine (Technical note), 733

Time, dose and fractionation factors for six fractions per week (Correspondence), 748

Misonidazole (Ro-07-0582) sensitizes mice to convulsions induced by hyperbaric oxygen or pentylenetetrazol (Correspondence), 1024

Scheduling of radiological equipment maintenance and generation of archival records using a mini-computer (Correspondence), 1026

CANCER CHEMOTHERAPY

The current role of cancer chemotherapy (Review article), 756

The effect of misonidazole on lymphocytes (Correspondence), 926

Care with radiosensitizers (Correspondence), 927

The neurotoxicity of misonidazole: pooling of data from five centres (Correspondence), 1023

Misonidazole (Ro-07-0582) sensitizes mice to convulsions induced by hyperbaric oxygen or pentylenetetrazol (Correspondence), 1024

ULTRASONICS

Clinical Aspects

Ultrasonic diagnosis of haematocervix following cone biopsy of the cervix (Case report), 56

The contribution of echography in the diagnosis of proptosis, 116

^{99}TC^{m}-fibrinogen as a thrombus-imaging agent (Correspondence), 139

Preparation of the patient for abdominal ultrasound scanning (Technical note), 387

Ultrasound and hepatic metastases, 596

Ultrasonic measurement of renal inclination; its importance in measurement of renal length (Technical note), 628

The B-scan ultrasonic appearances of gas in the biliary tree, 728

Prenatal ultrasonic diagnosis of fetal teratoma of the neck (Case report), 742

The value of real time ultrasound abdominal scanning (Correspondence), 748

Grey-scale ultrasound demonstration of ureterocele and hydroureter (Case report), 1016

Ultrasonic diagnosis of tuberculous peritonitis (Case report), 1018

Apparatus and Technical Aspects

A search for an effect of ultrasound alone and in combination with X rays on chromosomes *in vivo*, 46

Curve stripping of the third phase of the renogram in essential hypertension (Correspondence), 140

Preparation of the patient for abdominal ultrasound scanning (Technical note), 387
New grey tone rapid process films for ultrasound imaging (Technical note), 824
A comparison of grey-scale image recording systems, 968

NUCLEAR MEDICINE
Clinical aspects

Clinical radionuclide perfusion lymphangiography 35
Statements of the MRC Isotope panel (Correspondence), 58
Applicability of the "ten-day rule" to radiopharmaceutical investigations (Correspondence), 59
Curve stripping of the third phase of the renogram in essential hypertension (Correspondence), 140
Clinical trials of four pancreatic scanning agents, 206
Rectilinear bone scanning: differentiation between metastases and degenerative spinal disease, 281
The appearances of renal transplant lymphocoeles during dynamic renal scintigraphy, 342
Upper gastrointestinal tract visualization as an aid to the interpretation of pancreas scintigrams (Correspondence), 395, 396
Topographic relation between the myocardial uptake of radiothallium and left ventricular kinetics in myocardial infarction, 443
Thyroid uptake measurements: the influence of gland depth, gland mass and lobe separation, 454
Visualization of abnormal adrenal uptake of 19-iodocholesterol in Conn's syndrome (Case report), 545
The use of sodium chloride injection B.P. in the preparation of radiopharmaceuticals (Correspondence), 556
An evaluation of the use of ^{99}Tc^{m}–dimercapto-succinic acid (DMSA) as a static imaging agent, 599
Isotope renography and long term follow up of renal transplant patients, 802
Diagnosis of an ileal duplication with sodium pertechnetate ^{99}Tc^{m} (Case report), 825
Hepatobiliary imaging: a comparison of ^{99}Tc^{m}-dihydrothiotic acid and ^{99}Tc^{m}- pyridoxylidene glutamate in the non-jaundiced patient, 858
Hepatobiliary imaging: the use of ^{99}Tc^{m}-peridoxylidene glutamate scanning in jaundiced adults and infants, 862
The design of the detector and collimators of a hybrid scanner (Correspondence), 930, 931
ICRP 1977 recommendations and handling of radionuclide generators (Correspondence), 931
Limitations of the single sample tracer method for determining glomerular filtration rate, 981

NUCLEAR MEDICINE
Apparatus and Technical Aspects

A new gamma camera method for the measurement of thyroid uptake of technetium 99m pertechnetate (Technical note), 50
A technique for measuring the accumulation of ^{99}Tc^{m} stannous–ethane–1–hydroxy–1, 1–diphosphonate in the canine tibia (Technical note), 51
Experience with an automatic isodose plotter (Correspondence), 58
Statements of the MRC Isotope panel (Correspondence), 58, 395
Applicability of the "ten-day rule" to radiopharmaceutical investigations (Correspondence), 59
^{99}Tc^{m}-fibrinogen as a thrombus-imaging agent (Correspondence), 139.
Clinical trial of four pancreatic scanning agents, 206
A computer simulation study of optimal thyroid radiation protection during investigations involving the administration of radioiodine-labelled pharmaceuticals, 265
Thyroid uptake measurements: the influence of gland depth, gland mass and lobe separation, 454
Visualization of abnormal adrenal uptake of 19–iodocholesterol in Conn's syndrome (Case report), 545
An evaluation of the use of ^{99}Tc^{m}-dimercapto-succinic acid (DMSA) as a static renal imaging agent, 599
Mean skeletal dose factors for beta-particle emitters in human bone. Part I: volume-seeking radionuclides, 622
The design of the detector and collimators of a hybrid scanner (Correspondence), 930, 931
Limitations of the single sample tracer method for determining glomerular filtration rate, 981
The influence of size and radiopharmaceutical concentration ratio on the detection of abnormalities in clinical radionuclide imaging, 986
Improvement of scanner performance by subtraction of Compton scattering using multiple energy windows (Instrumental note), 1004

PHYSICS
Applied to Radiotherapy

Expansion of a negative pi-meson peak to cover a range of depths useful for radiotherapy, 41
Experience with an automatic isodose plotter (Correspondence), 58
Interface dosimetry (Correspondence), 60
Build-up and depth-dose characteristics of different fast neutron beams relevant for radiotherapy, 122
Tissue substitute material "mix D" (Correspondence), 141
Corrections for humidity (Correspondence), 141
Skin-sparing effect in fast neutron radiation therapy (Correspondence), 223
On the nature and significance of the radiation outside the beam in neutron therapy, 375
The photon attenuation and absorption properties of clear and white polystyrene (Correspondence), 397
The determination of anatomical cross-sections using a radiotherapy simulator, 448
Tissue-air ratios for whole body irradiation with cobalt 60 gamma rays (Technical note), 460
Dosimetry of cathetron applicators in intracavitary therapy, 507
Implementation of the Philips treatment planning system for use in radiation teletherapy, 613
A heavy particle comparative study. Part I: depth-dose distributions, 699
A heavy particle comparative study. Part II: cell survival versus depth, 704
A heavy particle comparative study. Part III: OER and RBE, 712
A heavy particle comparative study. Part IV: acute and late reactions, 720
Absorbed radiation dose in radiation synovectomy (Correspondence), 836

Applied to Radiodiagnosis

Penetrameter cassette calibration to 400 kV and effects of extra-focal radiation when measuring tube filtration, 29
New horizons in intensifying screen technology. (Proceedings of The British Institute of Radiology, May 20, 1977), 233
Display of cross sectional anatomy by nuclear magnetic resonance imaging, 273
Correlations in bone mineral measurement using polychromatic X rays (Short communication), 392
Increased filtration due to tungsten deposits inside the envelopes of X-ray tubes (Correspondence), 397
Reciprocity law failure with film/screen combinations for mammography (Technical note), 529
A phantom designed to compare the quality of various mammographic images (Technical note), 731
Optimum photon energies for the measurement of bone mineral and fat fractions (Correspondence), 750
Positioning errors in bone mineral measurement (Technical note), 821
Constancy of radiation output during diagnostic X-ray exposures, 867
Human whole body line-scan imaging by NMR (Short communication), 921
Reduction of radiation dose to patients in xeroradiography, 974
Reduction of X-ray output during life (Correspondence), 1026

Applied to Nuclear Medicine

Mean skeletal dose factors for beta-particle emitters in human bone. Part I: volume-seeking radionuclides, 622
Human whole body line-scan imaging by NMR (Short Communication), 921
The influence of size and radiopharmaceutical concentration ratio on the detection of abnormalities in clinical radionuclide imaging, 986
Improvement of scanner performance by subtraction of Compton scattering using multiple energy windows (Instrumental note), 1004

Applied to Other Aspects of Radiology (Ultrasonics, Thermography, etc.)

A computer simulation study of optimal thyroid radiation protection during investigations involving the administration of radioiodine-labelled pharmaceuticals, 265
Display of cross-sectional anatomy by nuclear magnetic resonance imaging, 273
Good thermal dosimetry is essential to good hyperthermia research (Technical note), 532

RADIOBIOLOGY

A search for an effect of ultrasound alone and in combination with X rays on chromosomes *in vivo*, 46
Effects of negative pions and neutrons on the growth of *vicia faba* bean roots, 127
The response of the mouse ear to heat applied alone or combined with X rays, 132
The RBE of megavoltage photon and electron beams (Short communication), 220
The response of skin to fractionated heat and X rays (Short communication), 221
Skin-sparing effect in fast neutron radiation therapy (Correspondence), 223
Response of selected tumour cell populations separated from a fibrosarcoma following irradiation *in situ* with fast neutrons, 291
Hyperthermic sensitization of mouse intestine to damage by X rays: the effect of sequence and temporal separation of the two treatments, 302
The therapeutic advantage of combined heat and X rays on a mouse fibrosarcoma, 307
Hypoxic cell sensitization by misonidazole *in vivo* and *in vitro*, 317
The radiosensitizing effect of metronidazole and misonidazole (Ro–07–0582) on a human malignant melanoma grown in the athymic mutant nude mouse, 381
A comparison of the biological effect of iodine 125 and tantalum 182 gamma rays using *vicia faba* roots (Short communication), 392
Elkind recovery and "sub-lethal damage": a misleading association? (Correspondence), 398, 399
The sensitivity of the human breast to cancer induction by ionizing radiation (Review article), 401
Mechanism of radioprotection by vitamin C (Correspondence), 473
Vitamin C and radioprotection (Correspondence), 474
Radiation damage to the rat spinal cord: the effect of single and fractionated doses of X rays, 515
The response of *E. coli* AB2463 recA to fast neutron beams with mean energies in the range 4 to 27 MeV, 524
A linear transform of the mutli-target survival curve (Technical note), 534
Measurements of the OER and RBE for neutrons generated by 70 MeV protons on lithium (Short communication), 550
Radioprotection of mammalian cells by procaine (Short communication), 551
An "error" in the "Pike-Alper" analysis (Correspondence), 557
Cytotoxicity and radiosensitization in mouse and man (Short communication), 636
Pitfalls in the use of *in vitro* survival curves for the determination of tumour cell survival with fractionated doses (Short communication), 637
Flagyl and radiation-induced chromosome breakage (Correspondence), 654
A heavy particle comparative study. Part II: cell survival versus depth, 704
A heavy particle comparative study. Part III: OER and RBE, 712
A heavy particle comparative study. Part IV: acute and late reactions, 720
The toxicity of the radiosensitizer misonidazole towards hypoxic cells *in vitro:* a model for mouse and man (Short communication), 745
The magnitude of hypoxic cell cytotoxicity of misonidazole in human tumours (Correspondence), 747
The tolerance of mouse tails to necrosis after repeated irradiation with X rays, 808
The effect of vitamin E on cellular survival after X irradiation of lymphoma cells (Short communication), 832
Vascular permeability in the ears of rats after X-irradiation, 895
The relationship between total dose, number of fractions and fraction size in the response of malignant melanoma in patients, 905
Radiation response of mice maintained on a defined diet (Short communication), 923
The effect of misonidazole on lymphocytes (Correspondence), 926

INDEX TO VOLUME 51

Care with radiosensitizers (Correspondence), 927
The effect of chronic reductions in the arterial partial pressure of oxygen on the radiation response of an experimental tumour, 992
The effect of vascular occlusion on the thermal sensitization of a mouse tumour, 997

HAZARDS AND RADIATION PROTECTION
Statements of the MRC isotope panel (Correspondence), 58, 395
Applicability of the "ten-day rule" to radiopharmaceutical investigations (Correspondence), 59
Gonad dose in cineurethrocystography, 210
Where should a film badge be worn? (Correspondence), 225, 557
Protection of the eye during carotid angiography, 262
A computer simulation study of optimal thyroid radiation protection during investigations involving the administration of radioiodine-labelled pharmaceuticals, 265
The sensitivity of the human breast to cancer induction by ionizing radiation (Review article), 401
X-ray dose received by patients in a population survey for colonic diverticular disease (Short communication), 472
Lead aprons and film badges (Correspondence), 475
Good thermal dosimetry is essential to good hyperthermia research (Technical note), 532
Thyroid irradiation and the new ICRP dose limits (Correspondence), 553
Safety, radiological equipment and the law (Proceedings of The British Institute of Radiology, January 20, 1978), 751
Radiation protection in dentistry (Correspondence), 837
CAT stimulation of retina (Correspondence), 837
Radiology now. The ten day rule—principles and practice, 843
Radiation exposure to the patient in computerized tomography (Correspondence), 925
ICRP 1977 recommendations and handling of radionuclide generators (Correspondence,)931
Automatic numbering punch for radiation protection films (Technical note), 1003

THERMOGRAPHY
The sensitivity of the human breast to cancer induction by ionizing radiation (Review article), 401

EDITORIALS
Instructions to authors, 79
Analysis of publication, 1977, 394
New home for The British Institute of Radiology (Editorial), 755

LECTURES AND ADDRESSES
Functional landscapes in the brain studied with regional blood flow measurements (MacKenzie Davidson Memorial Lecture, May 19, 1977), 657
Current thoughts on fast neutron therapy (MacKenzie Davidson Lecture, November 17, 1977) 943

PROCEEDINGS OF MEETINGS
Proceedings of the British Medical Ultrasonics Group (December 20 and 21, 1976), 226
Proceedings of The British Medical Ultrasound Society (December 7–8, 1977), 644
Proceedings of the Royal College of Radiologists (February 18, 1977), 477
Proceedings of The British Institute of Radiology Annual Congress (April 14–15, 1977), 62
Joint radiological meeting—Leeds (Proceedings of The British Institute of Radiology, September 24–25, 1976), 142
The Annual Congress, Scientific Exhibition (April 14–15, 1977), 154
New horizons in intensifying screen technology (Proceedings of The British Institute of Radiology, May 20, 1977), 233
Late effects on normal tissues (Proceedings of The British Institute of Radiology, November 18, 1977), 236
Unorthodox approaches to fractionation (Proceedings of The British Institute of Radiology, February 18, 1977), 478
Radiobiology work-in-progress meeting. (Proceedings of The British Institute of Radiology, February 17, 1978), 559
In vivo and *in vitro* radioisotope investigations of diseases involving the endochrine organs (Proceedings of The British Institute of Radiology, February 16, 1977), 640
Real-time ultrasound (Proceedings of The British Institute of Radiology, October 20, 1977), 642
Safety, radiological equipment and the law (Proceedings of The British Institute of Radiology, January 20, 1978), 751
The theory and practice of data display (Proceedings of The British Institute of Radiology, February 13, 1978), 838
Recent advances in hyperthermia research (Proceedings of The British Institute of Radiology, May 11–12, 1978, 933

AWARDS
The Institute Awards, 471

OBITUARIES
J. G. Stewart, 78
G. Simon, 159
K. E. Jefferson, 320
F. R. Berridge, 932
Captain T. W. Barnard, 1030

BOOK REVIEWS
Abdominal grey scale ultrasonography, 627
Acoustic instrumentation and characterisation of lung tissue, 621
Advanced exercises in diagnostic radiology. No. 10: The urinary tract, 813
Advances in neurosurgery—4. Lumbar disc. Adult hydrocephalus, 92
A guide to electrical hazards and safety standards, 40
An atlas of cardiology: electrocardiograms and chest X-rays, 549
An atlas of polytome pneumography, 698
An atlas of normal developmental roentgen anatomy, 973
Angiography of the human brain cortex, 1019
An introduction to the physics of nuclear medicine, 730
A practical approach to modern X-ray equipment, 912
A radiographic index, 1010
Atlas of cardiovascular nuclear medicine, 820
Atlas of grey scale ultrasonography, 598

INDEX TO SUBJECTS—continued

Biological and environmental effects of low-level radiation, 126
Biological effects of microwaves, 318
Biological effects of ^{224}Ra. Benefit and risk of therapeutic application, 952
Biomedical ultrasonics, 427
Bone marrow transplantation and other treatment after radiation injury, 523
Cancer and radiotherapy. A short guide for nurses and medical students, 212
Cardiac catheterization and angiocardiography, 787
Cesium-137 from the environment to man: metabolism and dose, 212
Chemotherapy of cancer, 316
Clinical lymphography, 752
Clinical radiobiology, 374
Computerised cranial tomography, 497
Computerized axial tomography (An anatomic atlas of serial sections of the human body. Anatomy–radiology–scanner), 280
Coronary angiography and angina pectoris, 16
Coronary heart disease: clinical, angiographic and pathologic profiles, 23
CRC handbook series in clinical laboratory science. Section A: Nuclear medicine, volume 1, 612
Cross-sectional anatomy: computed tomography and ultrasound correlation, 280
Current concepts in radiology, 290
Dermatologic radiotherapy, 202
Determination of absorbed dose in a patient irradiated by beams of X or gamma rays in radiotherapy procedures (ICRU Report 24), 4
Development of angiography and cardiovascular catheterization, 205
Dictionary of abbreviations in medicine and the health sciences, 962
Dictionary of medical ethics, 219
Encyclopaedia of urology V/1 Supplement, diagnostic radiology, 985
Endometrial carcinoma and its treatment: the role of irradiation, extent of surgery and approach to chemotherapy, 846
Environmental international (Journal), 980
Erkrankungen des Magens (Diseases of the stomach), 527
Exercises in diagnostic radiology—8. Diagnostic ultrasound, 447
Gallium-67 imaging, 854
Graphs and tables for use in radiology, 272
Growth kinetics of tumours (cell population kinetics in relation to the growth and treatment of cancer), 405
Grundlagen der medizinischen radiologie (The basis of medical radiology), 846
Handbook of clinical nuclear medicine, 752
Hip arthrography, 857
Ichiban (Radiation dosimetry for the survivors of the bombings of Hiroshima and Nagasaki), 316
Introduction of nuclear radiation detectors, 835
Introductory physics of nuclear medicine, 621
Invasive radiologic diagnostic procedures, 991
Ionizing radiation metrology, 687
Lymphoreticular disease, 332
Manuel de techniques radiographiques du crane, 350
Manual on radiation protection in hospitals and general practice. Vol. 4: radiation protection in dentistry, 57
Medical radiation exposure of pregnant and potentially pregnant women, 380
Medical radionuclide imaging, 798
Monographie des annales de radiologie. 14. La myélographie opaque, 442
Myelography. Text book and atlas, 1022
Neuroradiology based on neuropathology (Neuroradiologie euf neuropathologischer Grundlage), 670
Neuroradiology. Case studies, 727
Nuclear cardiology: principles and methods, 655
Nuclear medicine: clinical and technological bases, 523
Nuclear medicine—focus on clinical diagnosis, 427
Nuclear ophthalmology, 538
Obstetrical diagnosis by radiographic, ultrasonic and nuclear methods, 770
Osteoarthritis of the hip, 121
Paleopathological diagnosis and interpretation, 391
Pediatric oncologic radiology, 627
Pediatric radiology, 807
Pediatric radiology. Case studies, 356
Percutaneous transluminal angioplasty, 158
Planning and plutonium, 801
Practical atlas of cardiac scintigraphy, 388
Progress in nuclear medicine. Vol 4: Medical cyclotrons in nuclear medicine, 462
Progress in pediatric radiology. Skull, spine and contents. Part II, clinical aspects, 502
Quality control in nuclear medicine, 346
Radiation and cellular control processes, 131
Radiation exposure from consumer products and miscellaneous sources, 792
Radiation protection design guidelines for 0.1–100 MeV particle accelerator facilities: NCRP report No.51, 369
Radiobiological research and radiotherapy, 752
Radiographic contrast agents, 110
Radiography in obstetrics, 514
Radiologic anatomy of the brain, 217
Radiological atlas of common diseases of the small bowel, 259
Radiologic science: a workbook and laboratory manual, 318
Radiology and injury in sport, 506
Radiology for medical students, 595
Radiology of the liver, 493
Radiology of the skull and brain. Vol. III. Anatomy and pathology, 690
Radiopharmaceutical dosimetry symposium, 327
Recent results in cancer research. Vol.55. Cancer active immunotherapy, immunoprophylaxis and immunorestoration, 28
Recommendations of the International Commission on Radiological Protection (ICRP 26), 195
Roentgenologic diagnosis Vol. I and II, 219
Skeletal projections for diagnostic radiology, 538
Structural shielding design and evaluation for medical use of X rays and gamma rays of energies up to 10 MeV (NCRP Report 49), 34
Technology and interpretation of nuclear medicine procedures, 374
Textbook of radiologic technology, 362
The adult postoperative chest, 380
The fundamentals of X-ray and radium physics, 413
The handling, storage, use and disposal of unsealed radionuclide in hospitals and medical research establishments. (Annals of the ICRP, Vol. I, No. 2—ICRP Publication 25), 639
The hospital preparation of radiopharmaceuticals, 483
The mediastinum-radiologic correlations with anatomy and pathology, 840

The physical principles of diagnostic radiology, 391
The SI for the health professions, 687
Tomodensitometrie cranio-cerebrale (scanographie), 866
Tomography: physical principles and clinical applications, 272
Traite de radiodiagnostic. Tome XIX. Radiopediatrie, 835
Ultrasonics in clinical diagnosis, 121
Ultrasonography in obstetrics and gynaecology, 840
Ultrasound: its applications in medicine and biology, 854
Understanding radiography, 801
Use of ionizing radiation and radionuclides in human beings for medical research, training and non-medical purposes, 480
Xeroradiography in otorhinolaryngology, 874
X-rays: more harm than good? 98

ANNOTATIONS
Radiology Now
The ten day rule—principles and practice, 843

MISCELLANEOUS
A simple coding system for a diagnostic X-ray department, 20
Nomenclature in scanning investigation (Correspondence), 61
Television fluoroscopy—a necessity or an unsupportable luxury? (Correspondence), 139
SI Units (Correspondence), 225, 748, 929
The centigray as the SI unit of dose (Correspondence), 395
NSD, CRE, TDF and SI units (Correspondence), 473
Suggested terminology for scanning investigations (Correspondence), 473
Alterations in the manuscript of Röntgen's publication "Ueber eine neue Art von Strahlen" (1895) (Correspondence), 475
Retained surgical swabs: possible causes for errors in X-ray detection and an atlas to assist recognition, 691
Education in and status of, radiology in Europe, 834
Repression of the medical profession in Argentina (Correspondence), 925
Maintenance of "Graf pen" (Correspondence), 929
Medical iconography (Correspondence), 930
The discovery of X rays (Correspondence), 931
Scheduling of radiological equipment maintenance and generation of archival records using a mini computer (Correspondence), 1026
SI units and dimensions of NSD, CRE and TDF (Correspondence), 1026

SPECIAL REPORTS
Sixth interim progress report of The British Institute of Radiology fractionation study of 3F/week versus 5F/week in radiotherapy of laryngo-pharynx, 241

REVIEW ARTICLES
Classification and radiographic features of uterine malformations: hysterosalpingographic study, 161
The sensitivity of the human breast to cancer induction by ionizing radiation, 401
Continental notebook. Review of the continental radiological literature, 481
The current role of cancer chemotherapy, 756

EDUCATION
The effect of radiology electives on career choice at McMaster University, 503
Education in, and status of, radiology in Europe, 834

Our CT scanner won't be outdated tomorrow.

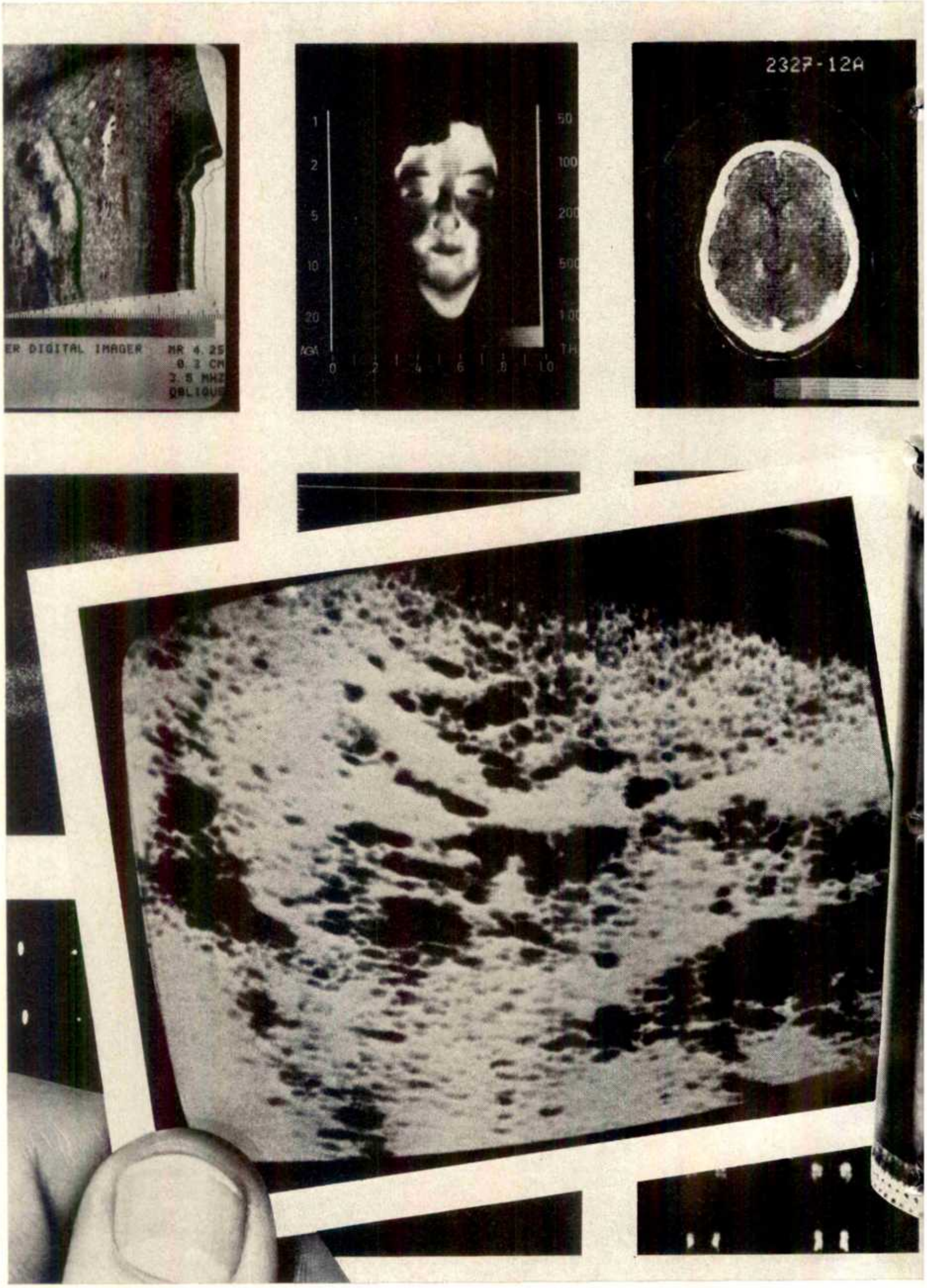
Philips TOMOSCAN 300 is the universal CT scanner designed and manufactured to give years of efficient and reliable service. Developed in close consultation with the medical profession, it meets all requirements for routine clinical practice.
The TOMOSCAN 300 features scan times as short as two and a half seconds, and offers geometrical enlargement for outstanding image quality in a variety of applications - whole-body, cerebral, and paediatric.
In addition, sophisticated patient positioning aids ensure rapid and accurate examination procedures.

Backed by a past that includes extensive experience in X-ray diagnostics, the TOMOSCAN 300 is the CT scanner with a future.

PHILIPS

PHILIPS Medical Systems

For detailed information write to: Philips Medical Systems, Eindhoven, The Netherlands


ER DIGITAL IMAGER
MR 4.25
0.3 CM
2.5 MHZ
OBLIQUE
1
2
5
10
20
AGA
0
2
4
6
8
10
50
100
200
500
TH
2327-12A

The diagnostic details. Instantly.

Nothing saves time like Polaroid instant photography.

You can have a fully developed picture for diagnosis from your CRT monitor in seconds.

For sheer convenience, too, there's no better way. You don't need developing and printing equipment. You don't need a darkroom or chemicals. You don't even have to leave the patient. Everything is taken care of by the self-processing film.

Part of our films' convenience is that you know instantly whether the picture you've taken is exactly right for your diagnostic needs. If not, you can retake it on-the-spot while the patient is still in place.

Polaroid self-developing films have the sensitivity, resolution, exposure latitude and grey scale capability to deliver excellent diagnostic photographs.

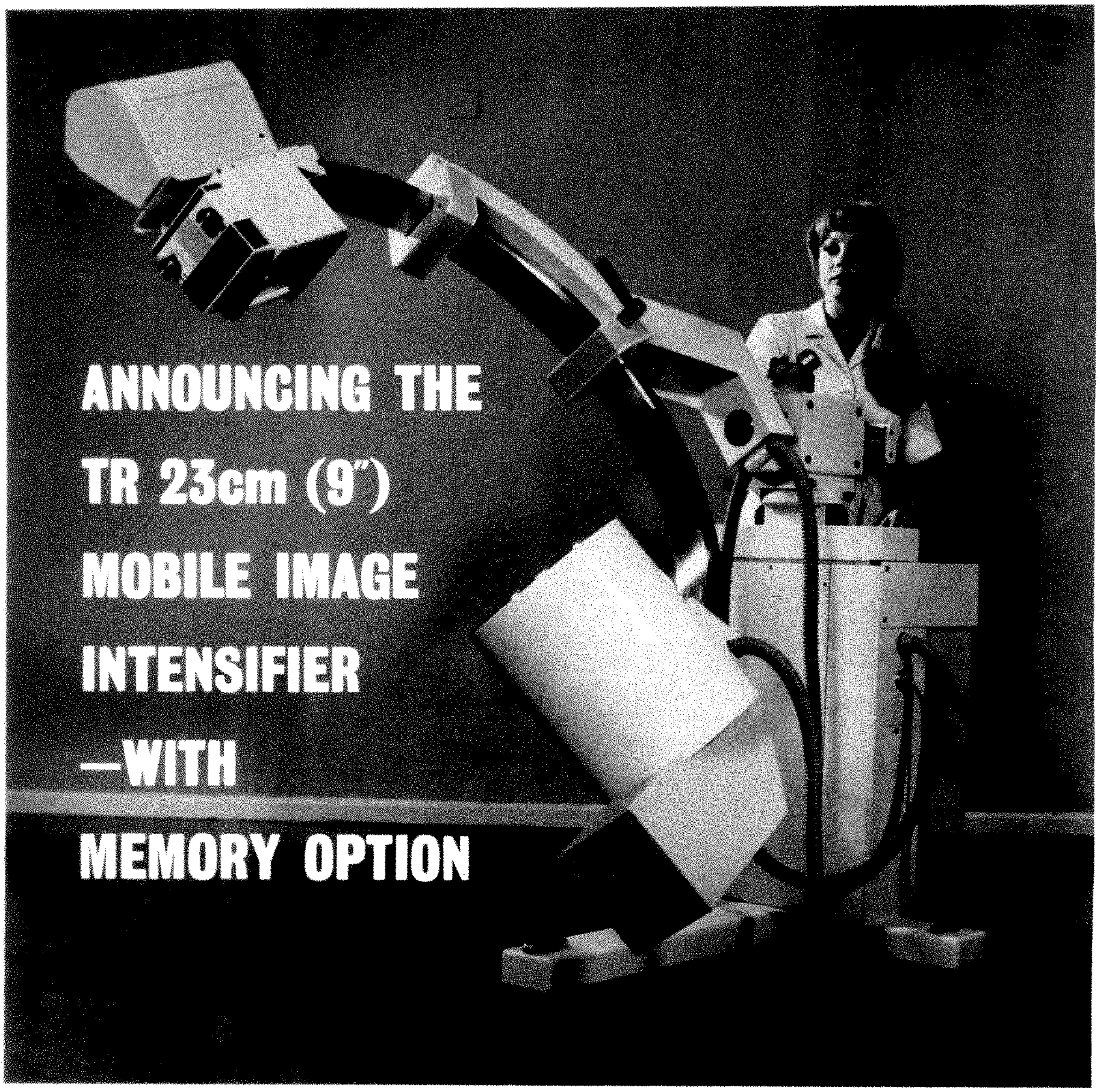
And one more thing – we offer you more than the speed, convenience and quality of our films. Our Technical Assistance is as close as your telephone. For more information call us on Freefone 2143 or write to Polaroid (UK) Ltd., Business & Professional Products Division, Ashley Road, St. Albans, Herts. AL1 5PR.

Polaroid

Instant films for CRT recording

'Polaroid' is a registered trademark of Polaroid Corporation,
Cambridge, Mass.,USA. Polaroid (UK) Ltd.,
Ashley Road, St. Albans, Herts. © Polaroid Corporation 1978.

Left: Ultrasound Scan. Longitudinal Examination.
Common Bile Duct and Hepatic Ducts. Patient has cancer of the Pancreas. Polaroid Type 667 film. Print size 3¼" x 4¼."



This low cost, high gain mobile image intensifier has been specially designed for surgical radiology.

The latest type 23cm intensifier brings the benefit of information over a larger field area.

The TV system includes image inversion facilities and a separate monitor on a trolley.

The X-ray tube provides up to 110kV for radiography and fluoroscopy.

A wide range of movements assists exact positioning around the theatre table.

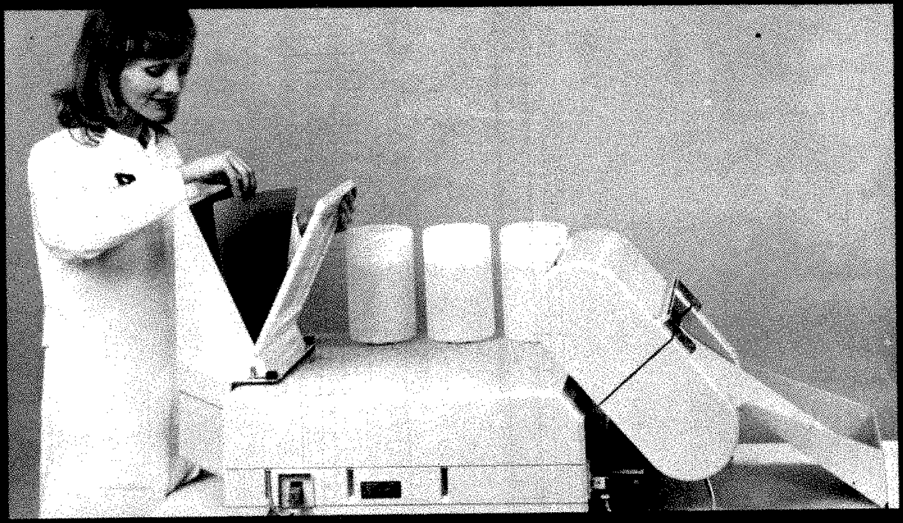
Optional extras include memory storage with special double monitor for simultaneous viewing of live and stored images.

For details of this unit and a budget 6in version, please contact

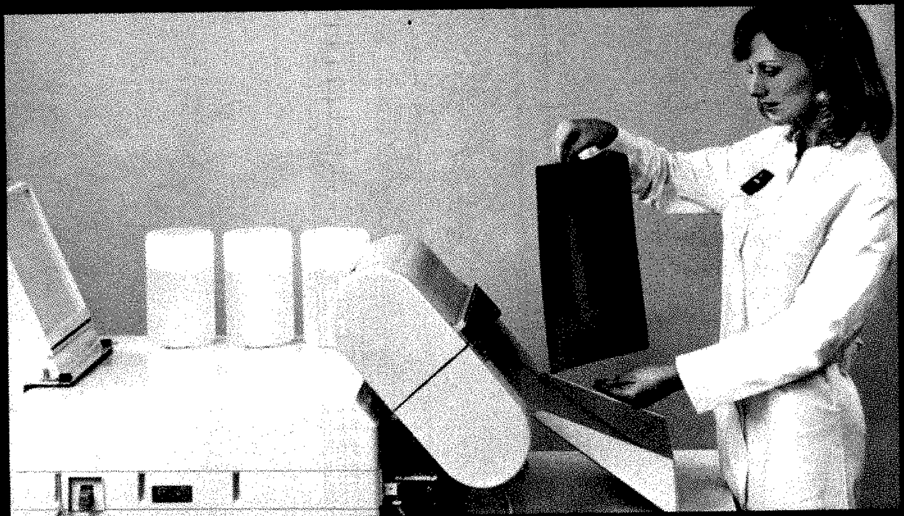
*Our 1978–9 catalogue is now available. Contact us and a copy will be mailed by return

TODD RESEARCH LTD
ROBJOHNS ROAD
CHELMSFORD CM1 3DP
TEL. 62233/7 TELEX 99327

GEVAERT AGFA-GEVAERT



In just two minutes...



you will understand why we have sold over 3000 Gevamatic 60's in only 2 years

The Gevamatic 60 is fast. Give it just a few minutes to warm up, and it will process your film in two minutes – drying time included.

The whole process is automatic. Automatic replenishment, temperature control and drying, and continuous roller film-transport.

Safety thermostats guard against overheating of the baths and the dryer, and a special film guidance system prevents damage to the film.

Sound, simple construction and good design have made this desk-top unit one of the most successful X-Ray film processors ever marketed by Agfa-Gevaert. We'd be glad to send you details.

Agfa-Gevaert Ltd.,
Medical X-Ray Dept.,
27 Great West Road,
Brentford, Middlesex TW8 9AX.
Tel: 01-560 2131

Specialists (Radiology)

Australian Department of Veterans' Affairs

Queensland

Applications are invited from suitably qualified Medical Practitioners who possess relevant postgraduate qualifications and are eligible for registration as a Specialist in Queensland, Australia.

Both positions are located at the Repatriation General Hospital, Greenslopes, which is set in 28 acres of land on the slopes of Mt Stephens and is approximately 5 miles from Brisbane, the capital city of Queensland. Greenslopes is a 460 bed general hospital, affiliated with the University of Queensland as a teaching hospital for medical undergraduates, with Readers and Senior Lecturers in Medicine and Surgery. Accreditation in Medicine, General Surgery, Pathology, Radiology, Psychiatry, Anaesthetics, Dermatology and Rehabilitation has been granted to the hospital.

The successful applicants may be permanently appointed as Specialist (Radiology) or consideration may be given to fixed term employment for a period of two or three years with the option of negotiating an extension.

Duties:

The successful applicants will be responsible to the Senior Specialist-in-Charge for the performance of normal specialist duties as radiologists and will assist in the co-ordination and control of the specialty. They will also participate in the implementation of a training programme for trainee radiologists.

The opportunity will be provided for medical research projects and training in ultrasound diagnosis. It is expected that the occupants will actively participate in this work.

Salary:

$A24,444–33,266 per annum (at present exchange rate £1 = $A1.61).

The right of limited private practice is currently under negotiation.

Conditions:

Four weeks annual leave and generous sick leave are provided. Fares to Brisbane for the appointees and their families and an allowance until permanently housed may be paid. Some assistance may also be given towards the removal of household and personal effects.

Applications:

Applications including details of qualifications and experience should be forwarded to:

Deputy Commissioner
Department of Veterans' Affairs
Box 651, G.P.O.
BRISBANE, QUEENSLAND, AUSTRALIA 4001
by August 1, 1978.

Australia

A promise kept...

The new CD38 Mobile Capacitor Discharge X-ray Unit

We promised you a new mobile capacitor discharge unit. We've done even better. Our CD 38 incorporates the proven features of the well established and successful D 38 mobile with the added benefits of capacitor discharge.

Practical and easy to use

Compact self-propelled unit with telescopic tube column and cross-arm—combining easy operation, extensive tube movements and maximum stability.

High Output

kV—range continuous from 30-125 kV

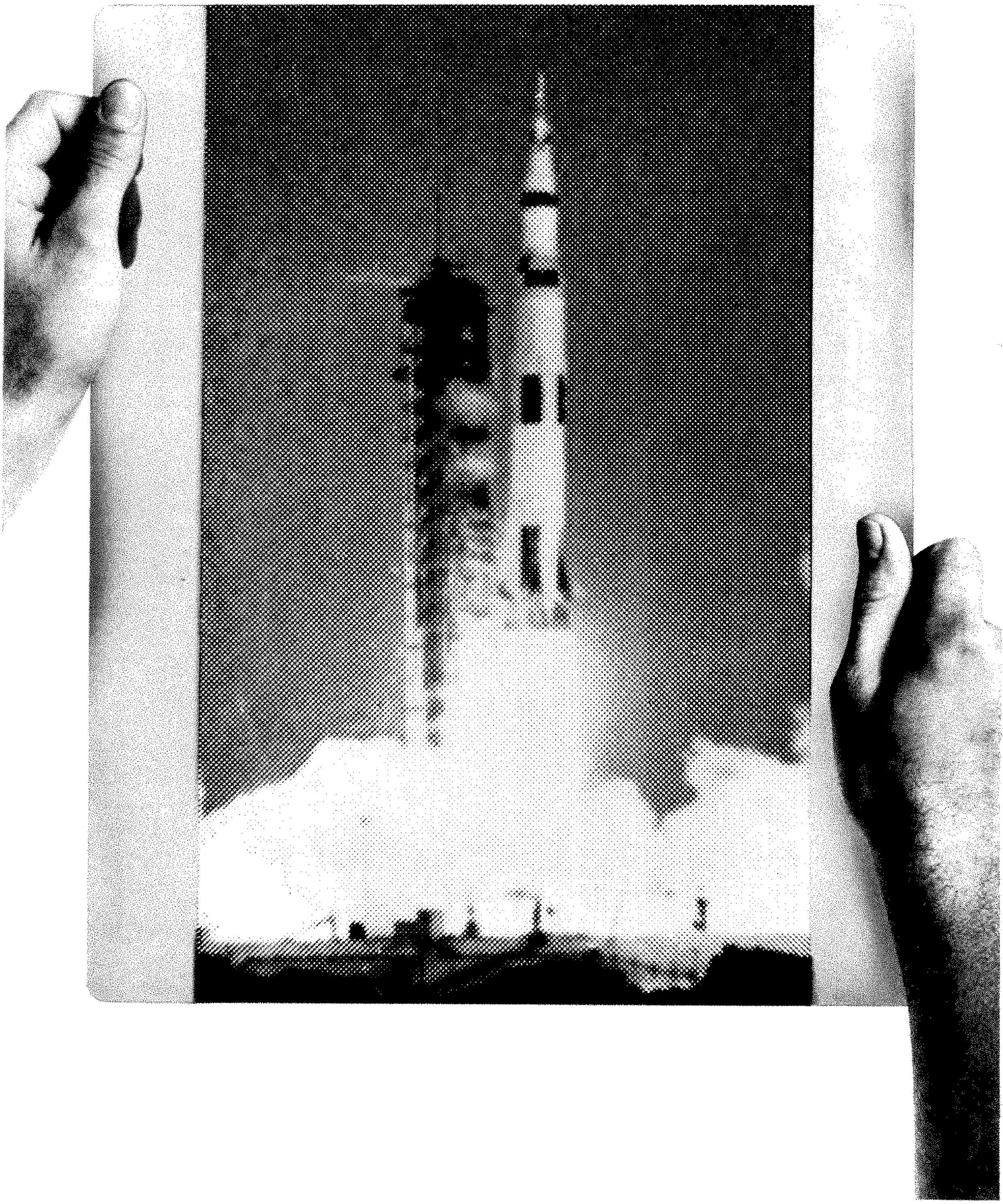
mAs—continuous selection from 4-50 mAs (250 mA maximum). Allows examinations usually restricted to static units.

Consistent results

The CD 38 will operate at full output from normal power supplies, producing consistent, high quality radiographs.

GEC
Medical

GEC Medical Equipment Limited,
East Lane, Wembley, Middlesex,
England HA9 7PR.
Telephone: 01-904 1288
Telex: 922177
Cables: Skiagram, Wembley.



ILFORD shows up everywhere.

The performance you expect – and get from ILFORD X-ray materials shows up in many other, sometimes unexpected places.

For if there's an image to be recorded, ILFORD will seldom be far away.

Our Microfilm products show up in the computer world recording output and in the fields of finance and industry with image retrieval systems. And again in the security recording of the massive weekly tide of football pool coupons.

We show up again in newspapers and magazines where ILFORD films and papers provide the illustrations which are often converted into print by ILFORD Graphic Arts materials.

Our Photographic products can show up everywhere from banks (Surveillance film for high security areas) to outer space (Nuclear emulsions as used in every U.S. space shot so far).

In Colour Printing too – amateur or professional – Cibachrome shows up wherever standards really count. You may not see the name, but you will see the results – everywhere.

It is this very involvement in so many fields that supports the broad fundamental research and keeps the ILFORD products you use efficient and up-to-date.

One last thing from ILFORD that always 'shows up': the after sales and technical service.

ILFORD X-RAY

ILFORD Limited, Basildon, Essex.

There's more to ILFORD than meets the eye

Your Kodak

rep wants to give you a helping hand

Give your rep a few minutes of your time.

And he'll help you expose a set of high definition extremity radiographs (like the one reproduced here) processed in your department in 90 seconds.

Give him a little longer and he'll demonstrate for you high information radiographs of all types. Ask him to tell you about any of these Kodak products for the radiographer.

Kodak 'Lanex' Regular Screens. This high speed rare earth system is exclusive to Kodak.

Kodak Ortho G Film. Colour sensitivity is matched to the 'Lanex' screens for optimum contrast, high information content and low dosages.

Kodak 'X-Omatic' Cassettes. Specially designed to expel air on closing, and provide excellent film/screen contact.

Kodak 'X-Omatic' Identification Camera, Model X-1-L. Allows the radiographer to record patient data on the radiograph at the point of exposure.

Kodak RP 'X-Omat' Processor, Model 101. Low cost, low noise, high speed automatic processing with cold water wash.

Kodak 'Min-R' Screen and Film. The fast, high definition film/screen combination for mammography, using rare earth phosphors.

Kodak RP 'X-Omat' Processor, Model M6A-W. Our fastest automatic processor, delivering roll and sheet film at about 167 cm per minute.

Whenever you need information, speak to your Kodak representative. You'll find he's got all the facts at his fingertips.

Kodak. We care about your image

Kodak

Kodak Lanex, X-Omatic, X-Omat, Min-R are trade marks.

WANTED

DIAGNOSTIC RADIOLOGIST

DIAGNOSTIC RADIOLOGIST required immediately to join a two-man group presently serving a 213 bed acute treatment general hospital, performing 46,000 examinations annually. Training in special procedures desirable. Direct enquiries together with curriculum vitae to Dr H. J. Flood, Director, Department of Radiology, St Josephs Hospital, Bayard Drive, Saint John, New Brunswick, Canada E21 3L6 Telephone 5066522620.

WANTED

DIAGNOSTIC RADIOLOGIST

required for group in large western Canadian city. Training in ultrasound, mammography and Nuclear Medicine an asset. Private clinic practice and hospital affiliation. Please reply to Box No. 7, British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

---

free university amsterdam

The **Faculty of Medicine** invites applications for the position of

radiologist

as staff member in the Diagnostic- Radiology Department (head: Prof.dr. B.A. den Herder) of the University hospital (Academisch Ziekenhuis der Vrije Universiteit).
Participations in teaching at all levels will be expected.
Candidates are expected to agree with the Christian charter of the University.

Detailed information may be obtained from Prof.dr. F.G. Bouman, acting medical director of the hospital, tel.number: The Netherlands 20 - 548 34 50.

Written applications should be addressed to the Personnel Department, P.O.Box 7161, Amsterdam, under ref.nr. 238-1108.

VU

CAPITAL TERRITORY HEALTH COMMISSION

CANBERRA HOSPITAL

DIRECTOR OF DIAGNOSTIC RADIOLOGY

Position No. 5941

This position is now vacant. Applicants must be Specialist Radiologists holding a higher qualification in Radiology and eligible for registration as a Medical Practitioner in the A.C.T.

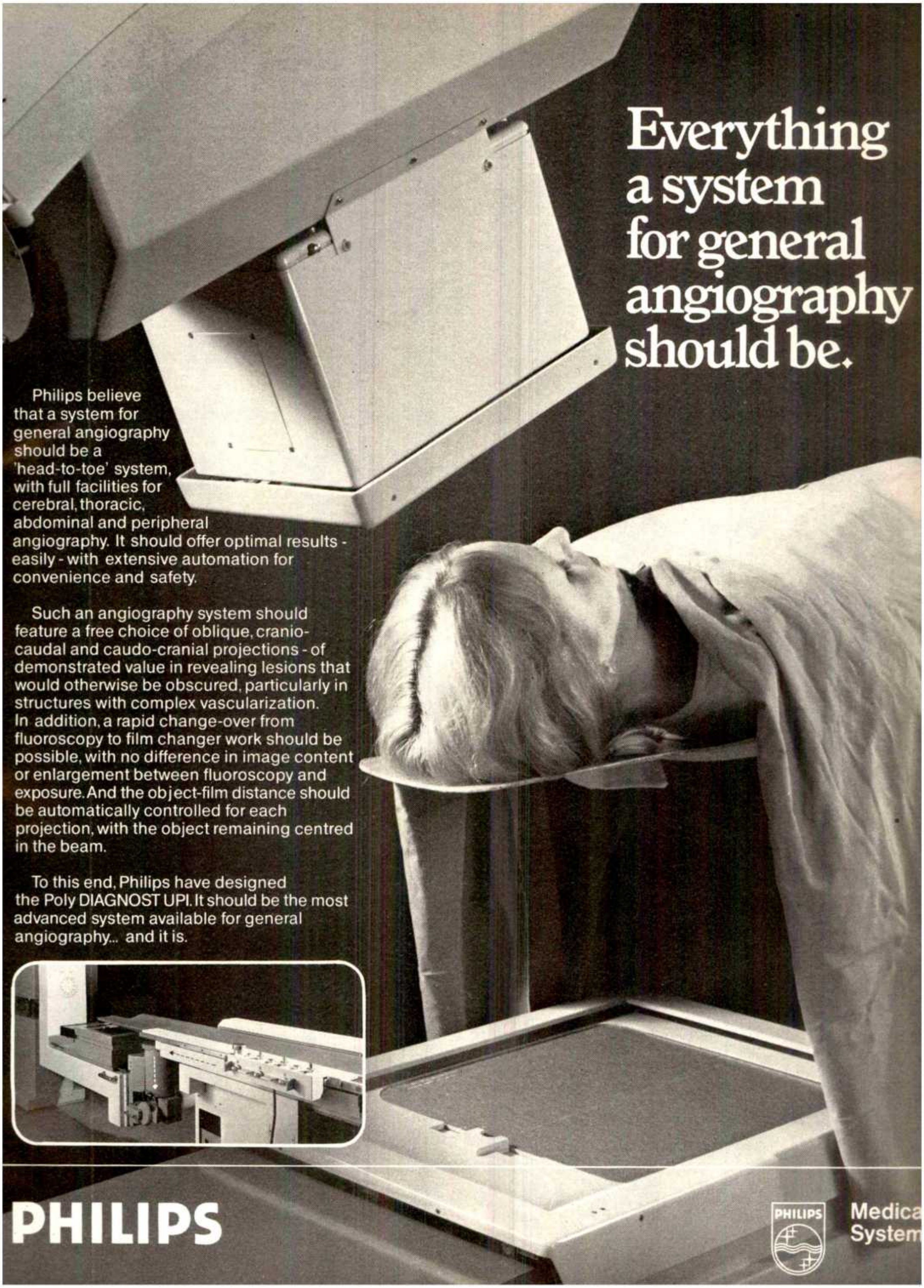
Canberra Hospital has 525 beds. It is an acute general hospital serving the northern half of the A.C.T. and acts as a specialist reference hospital for much of southern N.S.W. Most major specialities including obstetrics and paediatrics are represented in it and it is the major centre for accident and neurosurgical services. The X-ray Department is a modern one and its equipment includes an EMI brain-body scanner. It is approved for training purposes by the College of Radiologists of Australia.

Present Salary: Specialist, $24,444–$30,325 per annum.
Senior Specialist, $33,266 per annum.
Plus an In Charge allowance of $980 per annum.
Plus a limited right to private practice.

Conditions are in accordance with the Specialist Medical Officers' Agreement and Award, a copy of which will be sent to interested applicants.

Fur further information, contact the Chief Medical Administrator (Dr. A. F. Knyvett. Tel. (062) 432167).

Applications in writing should be directed to the Recruitment Officer, Canberra Hospital, Acton A.C.T. 2601 (Australia) and will be considered as soon as they are received.



Everything a system for general angiography should be.

Philips believe that a system for general angiography should be a 'head-to-toe' system, with full facilities for cerebral, thoracic, abdominal and peripheral angiography. It should offer optimal results - easily - with extensive automation for convenience and safety.

Such an angiography system should feature a free choice of oblique, cranio-caudal and caudo-cranial projections - of demonstrated value in revealing lesions that would otherwise be obscured, particularly in structures with complex vascularization. In addition, a rapid change-over from fluoroscopy to film changer work should be possible, with no difference in image content or enlargement between fluoroscopy and exposure. And the object-film distance should be automatically controlled for each projection, with the object remaining centred in the beam.

To this end, Philips have designed the Poly DIAGNOST UPI. It should be the most advanced system available for general angiography... and it is.

PHILIPS

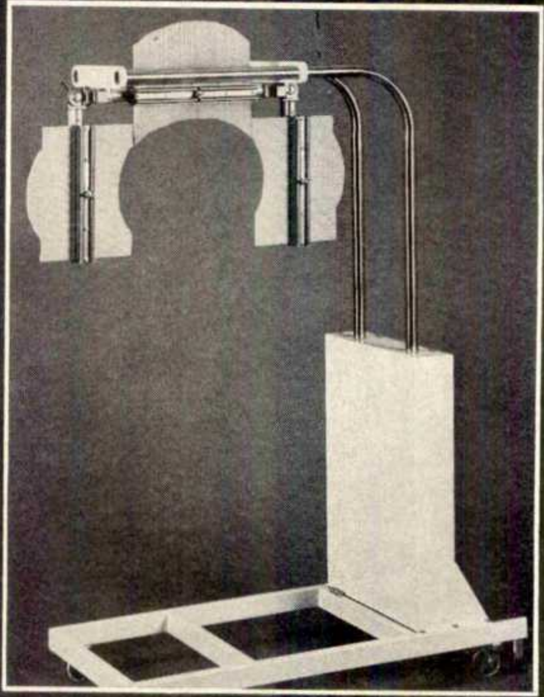
PHILIPS

Medica
System

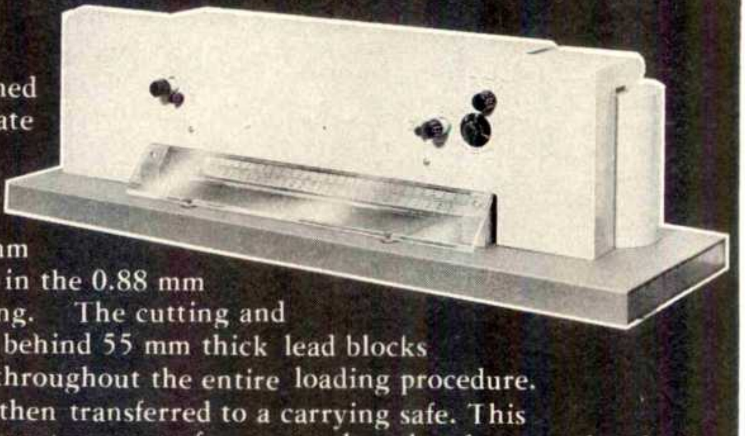
Formatron

The Formatron consists of 93 parallel anodised light alloy needles mounted between precision rollers. These rollers allow the needles to move freely and adjust accurately to the patient's profile. They are easily locked in position and when removed provide a perfect contour of the patient's outline.

A single Formatron may be used for small profiles. However, for a whole body contour, three Formatrons, mounted on a bracket assembly can be used. The three Formatrons can also be mounted on to an adjustable stand as illustrated and can be used in the Planning Room while the patient is in the supine position.



Iridium 192 wire encapsulator



The T.E.M. Instruments Limited Iridium 192 Wire Encapsulator has been designed to safely load and seal accurate lengths of 0.3 mm diameter Iridium 192 Wire into plastic tubing. Any length of wire from 5 mm to 300 mm can be cut and encapsulated in the 0.88 mm diameter technyl nylon tubing. The cutting and encapsulation is carried out behind 55 mm thick lead blocks which protect the operator throughout the entire loading procedure.

The encapsulated wire is then transferred to a carrying safe. This safe may be used for storage or transport of up to ten lengths of encapsulated wire.

TEM **TEM Instruments Limited**
Gatwick Road, Crawley, Sussex, RH10 2RG, England Tel 0293 31244
Telex: 87397, Grams: TESTMENT CRAWLEY

SIEMENS

Organomatic x-ray generators with everything worked out.

Siemens organ related programmes enable the setting-up time of x-ray generators to be reduced to just a few operations. They can be used for all diagnostic x-ray procedures, including rapid serialography.

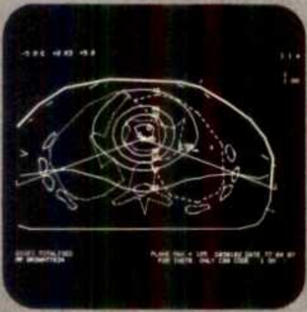
Three Organomatic units are available:–
Organomatic 506, a 6-pulse diagnostic x-ray generator/50kW; **Organomatic 502,** a 2-pulse unit/50kW; and the **Organomatic 306,** a 6-pulse, 30kW unit.

Special features of the range include 49 organ related programmes; 28 organ related planigraphic programmes; electronic kV regulation and non-blocking overload protection with organ related automatics. Up to four examination units can be connected.

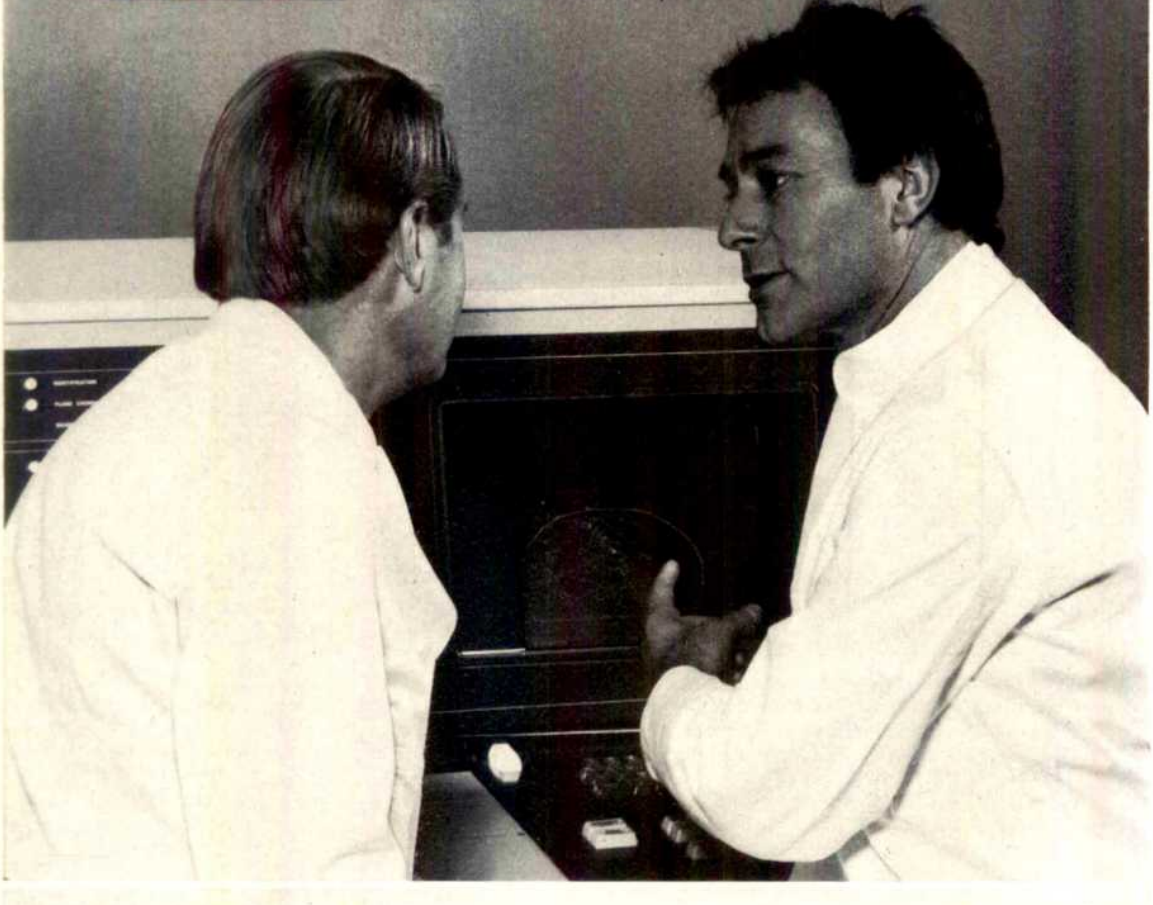
Siemens organ related x-ray generators have a great deal to offer. For full details contact:
Siemens Limited, Medical Group, Siemens House, Windmill Road, Sunbury-on-Thames, Middlesex TW16 7HS.
Telephone: 09327 85691.

In the world of x-ray generators Siemens has the answer.

Let's see what the TPS has to say about that.



Interaction – a dialogue between machine and therapist – was the fundamental design concept of the Philips Treatment Planning System (TPS). It is possible because the planning unit has its own computer – uninterruptedly available – which works from stored basic beam data and body cross sections fed in by tracing. The therapist can change treatment plans continuously, altering, for instance, technique, beam shape, or angle – seeing immediately the result of doing so. At any point he can go back and start again from the conditions of an earlier step – in fact he can consult the TPS much as he would a colleague. It can deal with any megavolt treatment unit and with brachytherapy. Progress towards optimisation is fast; treatment plans that once took days, take less than five minutes. Because it is so fast the computer has plenty of time to tackle other work for the department.

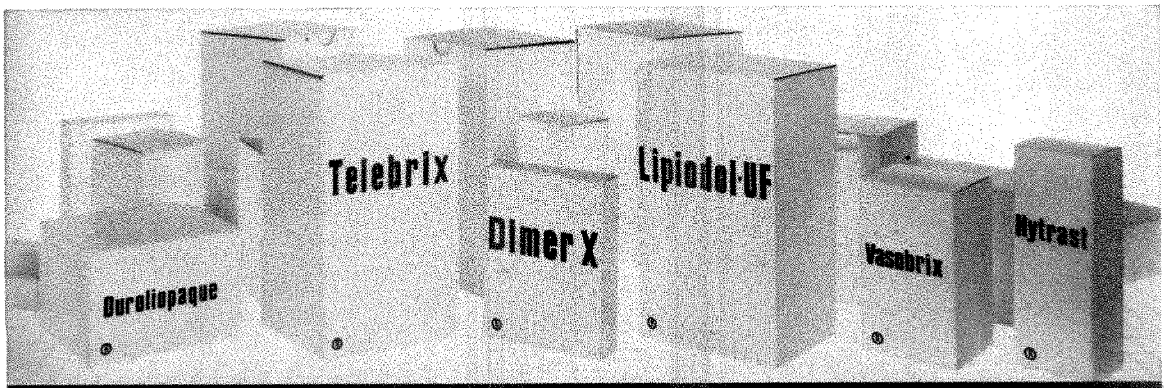


PHILIPS

N.V. Philips' Gloeilampenfabrieken
PCP/Medical Systems Division
Building QM, Eindhoven, The Netherlands

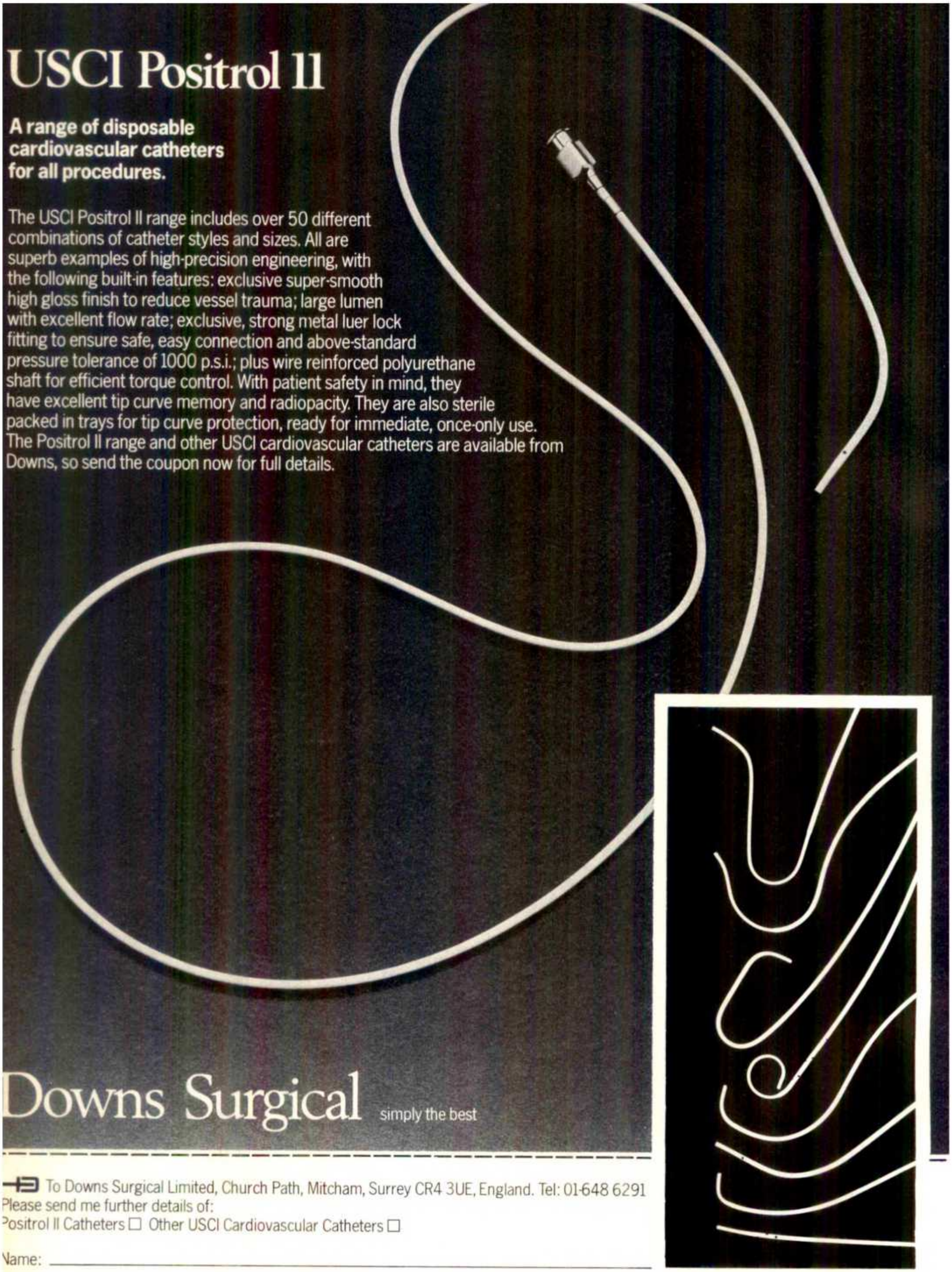
Philips Medical Systems Ltd.
45, Nightingale, Balham,
London SW12 8SX

Medical
Systems



WE MANUFACTURE
contrast
MEDIA
OUR
products
ARE
known
WORLD-WIDE
OUR
name isn't
GUERBET
BETTER CONTRAST MEDIA THROUGH RESEARCH

Laboratoire Guerbet, 16/24, rue Jean-Chaptal
93601 AULNAY-SOUS-BOIS Cedex - FRANCE
Telex : Guerbet 690682



USCI Positrol II

A range of disposable cardiovascular catheters for all procedures.

The USCI Positrol II range includes over 50 different combinations of catheter styles and sizes. All are superb examples of high-precision engineering, with the following built-in features: exclusive super-smooth high gloss finish to reduce vessel trauma; large lumen with excellent flow rate; exclusive, strong metal luer lock fitting to ensure safe, easy connection and above-standard pressure tolerance of 1000 p.s.i.; plus wire reinforced polyurethane shaft for efficient torque control. With patient safety in mind, they have excellent tip curve memory and radiopacity. They are also sterile packed in trays for tip curve protection, ready for immediate, once-only use. The Positrol II range and other USCI cardiovascular catheters are available from Downs, so send the coupon now for full details.

Downs Surgical simply the best

To Downs Surgical Limited, Church Path, Mitcham, Surrey CR4 3UE, England. Tel: 01-648 6291
Please send me further details of:
Positrol II Catheters ☐ Other USCI Cardiovascular Catheters ☐

Name: ____________________

Address: ____________________

Your Scintigraphy Kit

Your kit starts with any of our three simple one-step preparations which combined with our new Sterile Technetium-99m Generator offers a complete package for liver, lung, bone and brain scintigraphy. Later we will be adding more kits to our range.

All our kits are tested extensively in clinical trials which include the use of other technetium-99m generators as well as our own. All are terminally sterilized and every batch is animal tested.

Agent for Bone Scintigraphy

Our Technetium (MDP) Agent gives you the best skeletal visualization available today. The high bone uptake and rapid clearance from blood and soft tissue makes this superior to other bone agents giving better definition and improved discrimination.

New Agent for Lung Scintigraphy

Our new Technetium (MAA) Agent offers detailed lung visualization, with no interference from the liver. Particle size is strictly controlled with the majority in the range of 10–80μ.

New Agent for Liver Scintigraphy

The latest addition to our range is the unique Technetium (tin colloid) Agent. Its preparation is much simpler than sulphur colloid agents and requires no heating stage. It will visualize liver and spleen and unlike agents based on phytate, the colloid is formed in the vial, allowing quality control checks prior to injection.

The Radiochemical Centre Amersham

The Radiochemical Centre Limited, Amersham, England. Tel: Little Chalfont (024 04) 4444.
In W. Germany: Amersham Buchler GmbH & Co, KG, Braunschweig. Tel: 05307-4693-97.

1389/11/77

Partnership available private practice South Africa. **Diagnostic Radiologist** wanted to join well established private practice situated in coastal city with ideal climate. Hospital connections and scope for special investigations. Easy office hours and guaranteed income. Would suit a senior consultant or retired radiologist desiring regular light duties. Terms and conditions to be mutually arranged.

Curriculum Vitae to Box No 11
The British Journal of Radiology,
32 WelbeckStreet, London W1M 7PG.

Slotervaart Hospital
Louwesweg 6 Amsterdam
The Netherlands

DIAGNOSTIC RADIOLOGIST

required as locum tenens for ½–1 year.
Applications with curriculum vitae, qualifications and previous experience should be sent to the Directors of the Slotervaart Hospital.
The Slotervaart Hospital is a new 700-bed municipal hospital.

ANNOUNCEMENT

The Departments of Radiology and Continuing Education of The Harvard Medical School Announce Three Postgraduate Courses

COMPUTED BODY TOMOGRAPHY FOR THE DIAGNOSTICIAN
SEPTEMBER 25–28, 1978
Copley Plaza Hotel, Boston, MA

CHEST DISEASE: 1978 AN INTERDISCIPLINARY APPROACH WITH EMPHASIS ON RADIOLOGY
OCTOBER 16–20, 1978
Hyatt Regency Hotel, Cambridge, MA

ANGIOGRAPHY: 1978 ANGIOGRAPHY IN THE ERA OF THE NEW TECHNOLOGIES
OCTOBER 23–26, 1978
Hyatt Regency Hotel, Cambridge, MA

For further information, please contact Herbert L. Abrams, M.D. Cook Professor and Chairman, Department of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115. (617) 732–6273

The British Journal of Radiology
SUPPLEMENTS

	Price	*Members price*
No.1 **Certain aspects of the action of Radiation on Living Cells** edited by F. G. Spear (1946)	**£1·00**	**£1·00**
No.2 **Some Applications of Nuclear Physics to Medicine** by W. V. Mayneord (1950)	**£2·50**	**£1·75**
No.4 **Cancer of the Breast** by D. W. Smithers, P. Rigby-Jones and D. A. G. Galton (1952)	**£1·50**	**£1·00**
No.9 **The Spectra of X Rays Scattered in Low Atomic Number Materials** (1960)	**£1·00**	**£0·50**
No.11 **Central Axis Depth Dose Data for Use in Radiotherapy** edited by M. Cohen, D. E. A. Jones and D. Greene (1972)	**£4·70**	**†£3·20**
No.12 **Carcinogenesis and Radiation Risk: a Biomathematical Reconnaissance** by W. V. Mayneord and R. H. Clarke (1975)	**£6·50** ***£4·75**	**£4·75**
No.13 **The Pathogenesis of Reflux Nephropathy** by Prof. C. J. Hodson, T. M. J. Maling, P. J. McManamon and M. G. Lewis (1975)	**£1·90**	**£1·75**

*Special price for individual users, 1 copy only
†Special price also available to members of the Hospital Physicists' Association

Available from the Publications Office
The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG

AXISCAN 5

The new portable real-time ultrasound scanner from Kontron Roche

• Built to a unique design, offering all the facilities you require for obstetric and general abdominal scanning • Truly portable design makes it very easy to use in ante-natal clinics and other departments within hospitals • Simple operation facilitates routine obstetric investigations with the minimum of fuss • Fetal maturity estimations can be established quickly using the integral electronic calipers which automatically reproduce an on-screen digital display. • Results are permanently recorded with the built-in camera. • The excellent grey-scale display shows moving structures up to 25 cm deep. • All our customers are backed by a national 24 hour Kontron Roche service.

KONTRON ROCHE

serving hospitals throughout the world

For further information, please complete the coupon below and post to Dr. Hargreaves, Kontron Instruments Ltd., P.O. Box 188, Watford WD2 4YX or telephone Watford (0923) 47666

Please contact me to arrange a demonstration of/send me further information about/ the Axiscan 5.

NAME. . . . .

POSITION . . . .

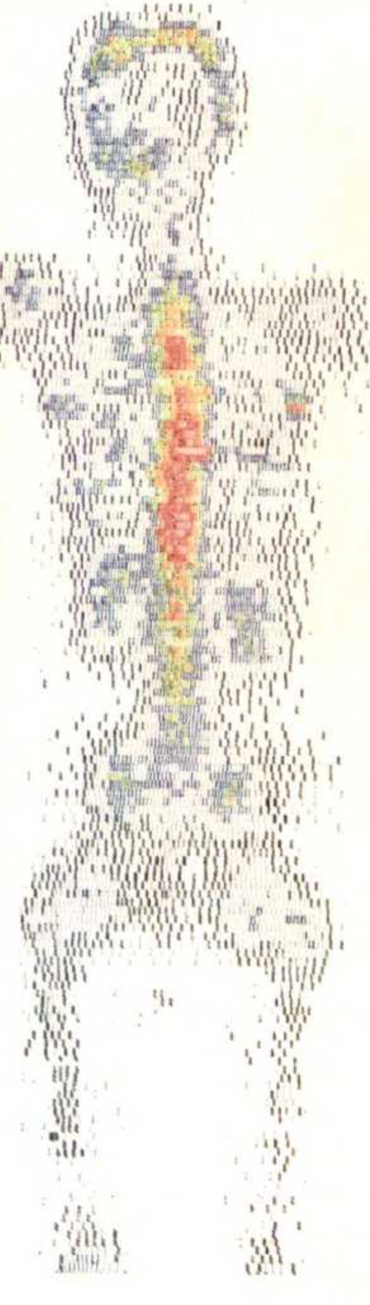
ADDRESS. . . . .

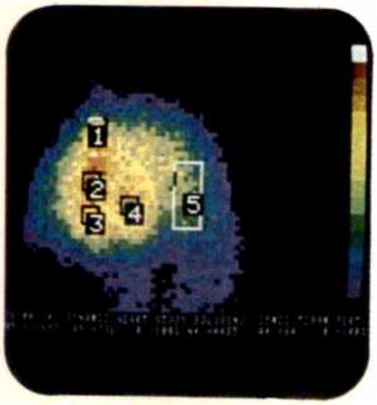
. . . .

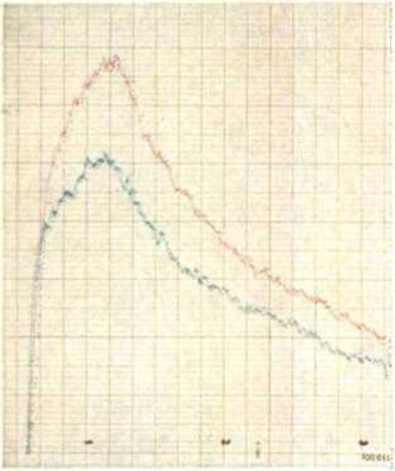
. . . .

TELEPHONE . . . .

Overall evidence







PHILIPS Medical Systems

This total body scan, dynamic heart study and kidney function, contribute only part of the overall evidence of Philips total capability in nuclear medicine. For in addition to developing, manufacturing and supplying the specialised equipment, we provide a complete range of services to back it all up.

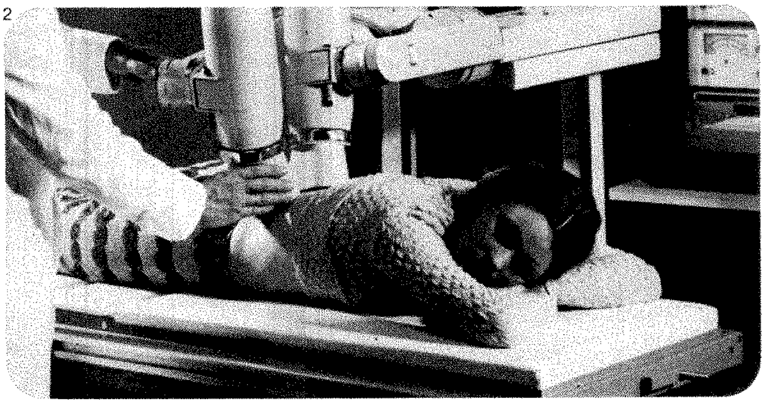
Expert guidance in the organisation and layout of your nuclear medicine department; objective advice about the most appropriate equipment to use; information on protective measures in line with general regulations.

Once decisions are made, we will install and commission the equipment and instruct you and your staff on its use. And if ever breakdowns do occur, we've an international network of specialised technicians who are always on call.

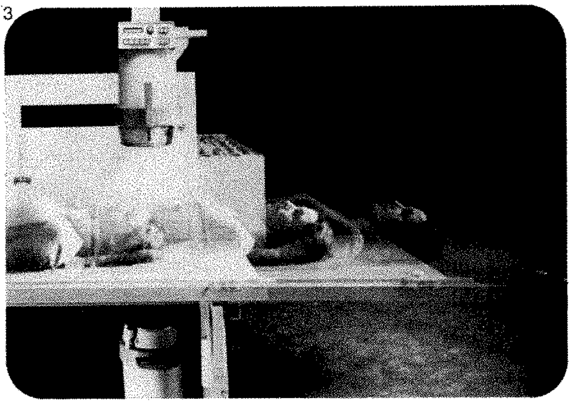
The whole programme is based on intensive medical-electronic research and extensive knowledge and experience in the field of medical diagnostics. That's the overall evidence Philips offer for progress in nuclear medicine.

1

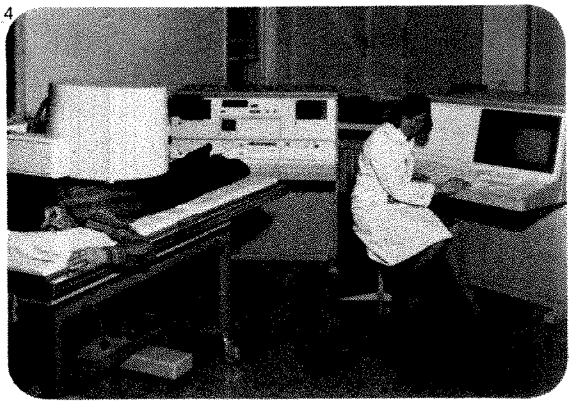
2



3



4



The range of equipment in Philips Nuclear Medicine Programme include a **Microcuriemeter** for rapid calibration of prepared radio-pharmaceuticals prior to patient administration, as well as **Automatic Sample Changers** (photo 1 shows the 100 sample version).

The sample changers form part of an integrated series of Function Measuring instruments comprising **Counter/Timers** (with optional printer control and background subtraction), a **Gamma Analyser** combining Isotope Selector, Pulse height Analyser, H.T. supply and Ratemeter, and single and dual-channel **Chart Recorders.** There is a choice of single or dual-channel systems - Renography for example (photo 2) - plus a **Lead Castle** for measurement in-vitro.

Total body scanning (photo 3) is an optional feature of the Philips **Universal Scintillation Scanner.** Based on modular design principles, it can be supplied in a variety of configurations from a basic single detector scanner to a dual-channel installation offering facilities for photo-scan, profile scanning and 4-track compact-cassette recording and playback.

The **Gamma Camera** (photo 4, left) features a selection of collimators for a wide variety of applications, and an output for connection of peripherals such as a data **Processing and Display System** (photo 4, right). Designed specifically to provide rapid quantitative and qualitative diagnostic information, Philips PDS employs a mini computer with disc-operated software programs. A FORTRAN option extends system capability. There is no specialised knowledge of data processing techniques required for program execution.

COUPON

If you would like further evidence on our nuclear medicine program, complete this coupon and send to: Philips Industries. Medical Systems Division, Building QM, Room 326, Eindhoven, The Netherlands.

Company: ____________________

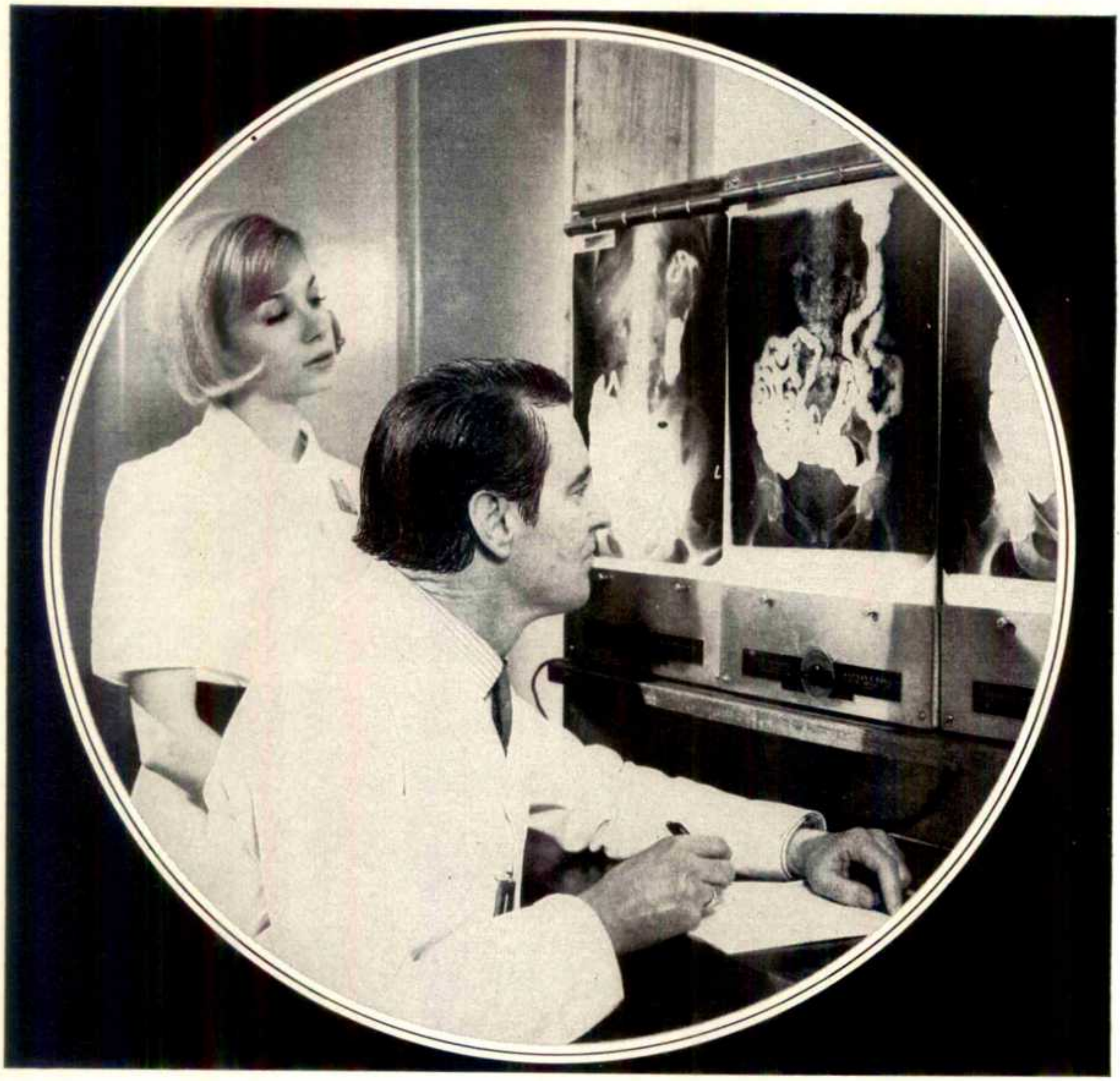
Name/Position: ____________________

City/Country: ____________________

Street/P.O. Box: ____________________

PHILIPS

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd
45 Nightingale Lane London SW12 8SX



True qualities that come as a revelation

Conray contrast media

The dependable qualities and wide scope of 'Conray' contrast media have been clearly demonstrated throughout many years of use in the field of radiodiagnosis. 'Conray' offers a choice of formulations designed to provide wide margins of safety and comfort for the patient together with optimum visualization in a comprehensive range of procedures and techniques.

'Conray'* contrast media are formulations of meglumine iothalamate, sodium iothalamate or combinations of the two.

*trade mark of Mallinckrodt Inc.
Further information is available in the data sheet
May & Baker Ltd Dagenham Essex RM10 7XS

M&B May&Baker

A member of
the Rhône-Poulenc
Group of Companies

MA 6335

Step into the future with the DIAGNOST 120

The DIAGNOST 120 - Philips remote-controlled diagnostic system - has been designed to meet tomorrow's requirements . . . as well as today's.

That means ensuring consistently first-rate image quality, whatever the recording technique. So every component in the imaging system has been carefully designed to the highest standards, giving you such advantages as an outstanding X-ray beam collimator, a very short tabletop-film distance, a new generation image intensifier. Universality is a requirement too; here, the DIAGNOST 120 provides you with facilities for a host of examination techniques. Any system offering so much is inevitably sophisticated - but the DIAGNOST 120 is also surprisingly easy to operate. Try it for yourself.

The logically arranged controls, continuously variable speeds for all movements, and high degree of automation let you concentrate on the patient. The result? You obtain the necessary diagnostic information, quickly and efficiently.

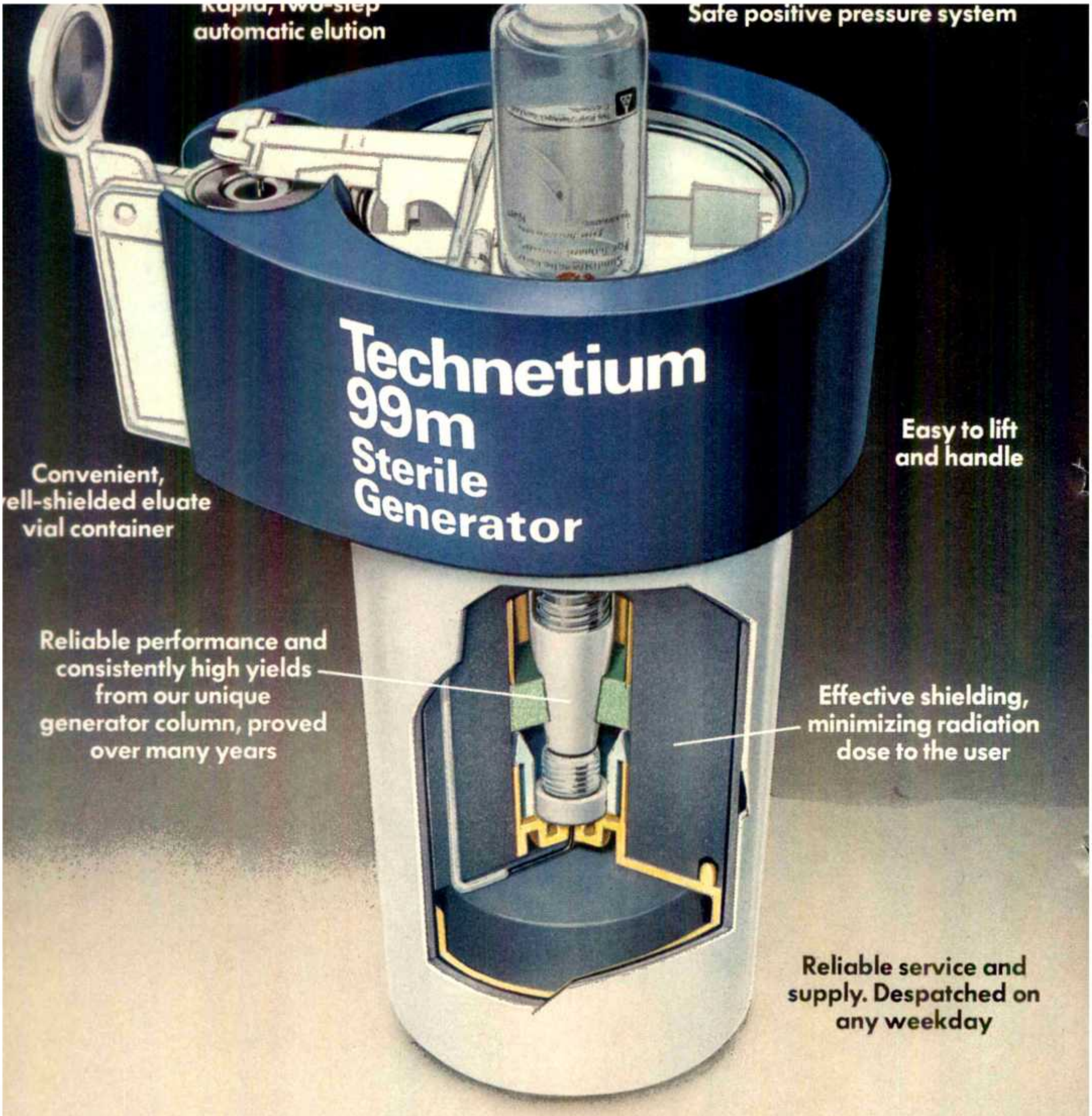
Despite its futuristic specification, the DIAGNOST 120 is available now. Why wait for tomorrow?

PHILIPS

PHILIPS

Medical Systems

or detailed information, write to: Philips Medical Systems, Eindhoven, The Netherlands
r Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8SX.

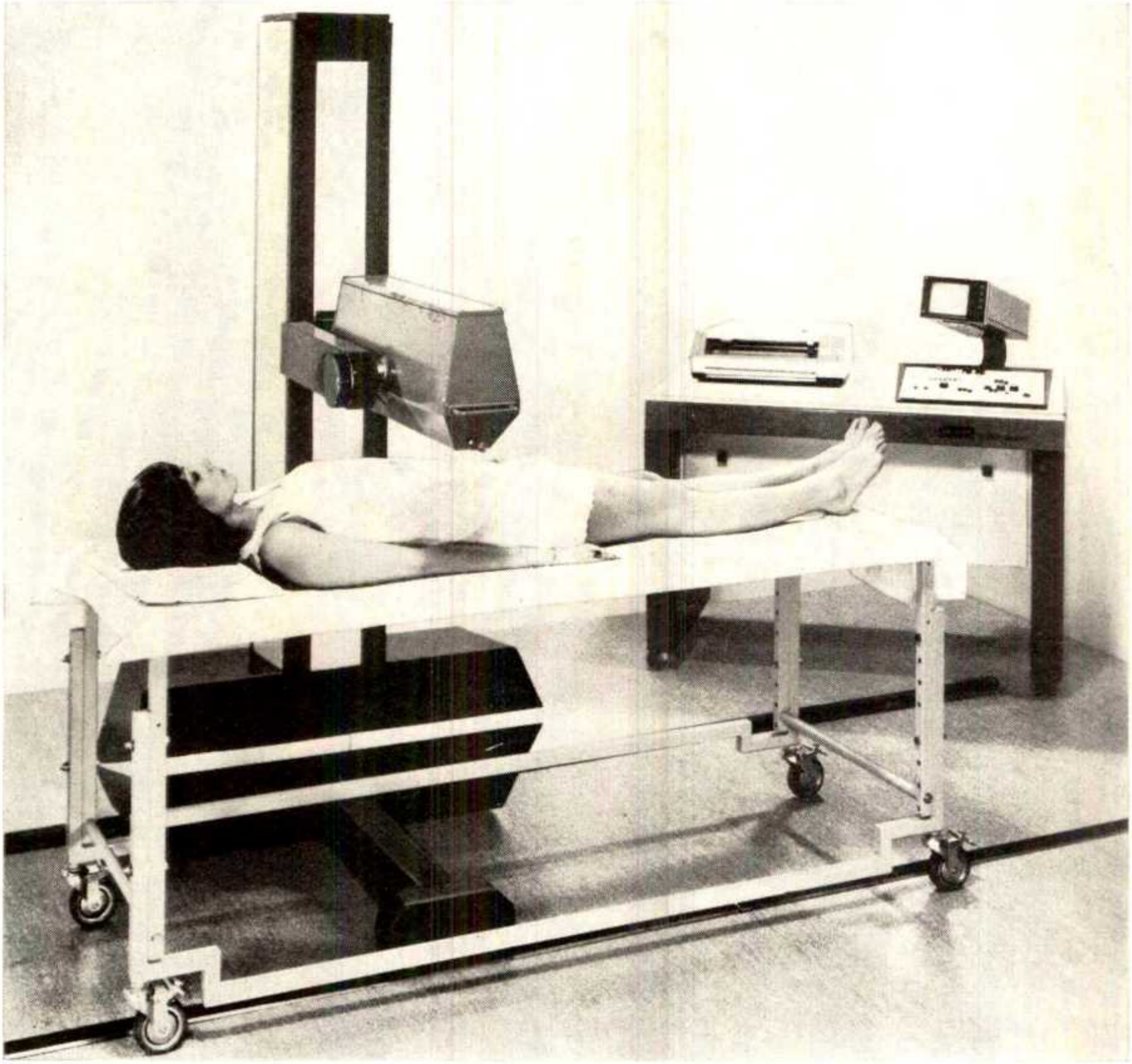

Rapid, two-step automatic elution
Safe positive pressure system
Technetium 99m Sterile Generator
Easy to lift and handle
Convenient, ell-shielded eluate vial container
Reliable performance and consistently high yields from our unique generator column, proved over many years
Effective shielding, minimizing radiation dose to the user
Reliable service and supply. Despatched on any weekday

Introducing our second generation generator

The Radiochemical Centre Amersham

The Radiochemical Centre Limited, Amersham, England. Tel: Little Chalfont (024 04) 4444
In West Germany: Amersham Buchler GmbH & Co KG, Braunschweig. Tel: 05307-4693-97

The universal instrument for static imaging



SCANICAMERA

from

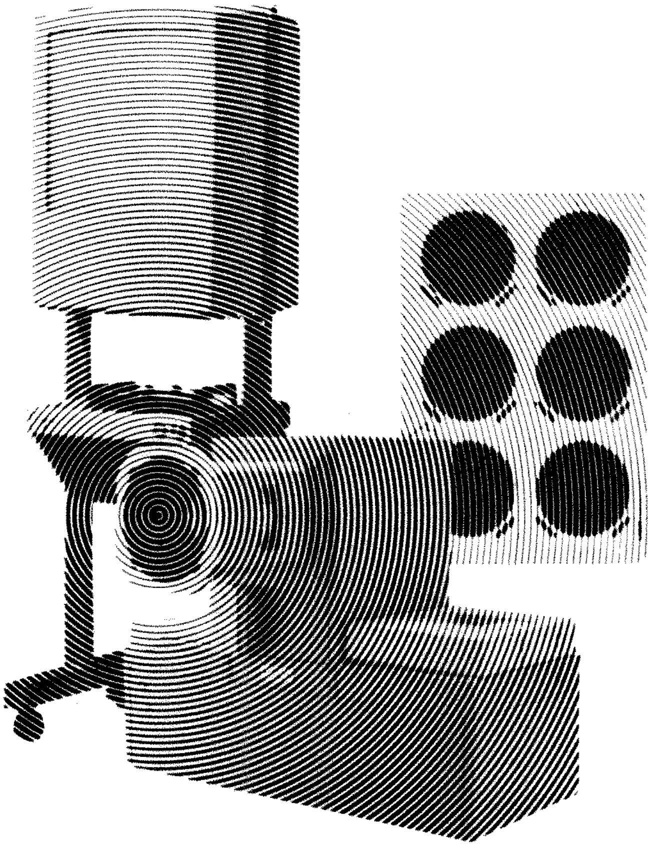
The linear design of the head of the Scanicamera makes it possible to obtain a rectilinear scintigraph with a movement in only one direction. Examination times are a quarter that of conventional scanners and are combined with improved image and quality.

Full details and specification from:
CGR MEDICAL LIMITED
Astronaut House, Feltham, Middx. Tel: 01-890 8166

40 years of experience and expert knowledge can be made yours very easily

Oldelft

Oldelft England ltd
16 Barclay Road, Croydon CRO 1JN
Tel. (01) 681 1171, telex 946154



The Anodica image intensifier camera, Helio viewer, Cadrix viewing frame and Delcomat copier shown here are part of the **Oldelft 100 mm sheetfilm system for spotfilm photography** which covers every single procedure in the handling of x-ray films: **exposure, processing, viewing, copying, framing, filing.**
Each piece of equipment can be purchased singly and fitted into existing routines.

Radiodiagnosis
Odelca x-ray cameras
100 mm System for spotfilm photography
Deltorax chest film changer
Odelscope image intensifier for fluoroscopy

Ultrasound
Real time linear phased array systems
Cardiac phased array sector scanners
General purpose gray-scale compound scanners

Nuclear medicine
Gamma cameras with complete range of accessories (e.g. multi-imager, whole body scanning bed)

Radiotherapy
4 and 15 MeV linear accelerators
Cobalt units

Radiotherapy planning
Simulix-Y simulator with Simtomix accessory for analog whole body tomography

Pulmonary function testing
Computerized equipment for the pulmonary lab
Automated procedures in spirometry, flow/volume loop analysis and exercise testing

Head Office: Holland, (nv Optische Industrie De Oude Delft), 2612 xe Delft, Postbox 72, Tel (015) 13 29 23, 12 40 44 Telex 32 384.
België/Belgique 2100 Deurne, Twee Gezusterslaan 34, Tel (031) 24 93 05.

Deutschland D 6300 Giessen/Lahn, Postfach 5420, Tel (0641) 4 10 49.
España Madrid 16, Uruguay 13, Tel (01) 259 1698.
France 91403 Orsay, B P 86, Tel (01) 907 5900.
Italia 00146 Roma, Via della Vasca Navale 84, Tel (06) 55 84 311.

Japan Osaka, Postbox 1042, Tel (06) 309 09 61.
Sverige 17206 Sundbyberg 6, Postbox 670, Tel (08) 98 38 95.
Schweiz 8618 Oetwill am See, Zelglistrasse 5, Tel (01) 92 91 318.
USA Fairfax, Virginia 22030, 2735 Dorr Avenue, Tel (703) 573 7020

BJR Supplements

No.1	*Certain aspects of the action of radiation on living cells,* edited by F. G. Spear (1946)	£1·00
No.2	*Some applications of nuclear physics to medicine,* by W. V. Mayneord (1950)	£2·50 (Members £1·75)
No.4	*Cancer of the breast,* by D. W. Smiths, P. Rigby-Jones and D. A. G. Galton (1952)	£1·50 (Members £1·00)
No.9	*The spectra of X rays scattered in low atomic number materials,* by W. R. Bruce and H. E. Johns (1960)	£1·00 (Members 50p.)
No.11	*Central axis depth dose data for use in radiotherapy,* edited by M. Cohen, D. E. A. Jones and D. Greene (1972,1st reprint 1974, 2nd reprint 1978)	£4·70 (Members £3·20) *
No.12	*Carcinogenesis and radiation risk: a biomathematical reconnaissance,* by W. V. Mayneord and R. H. Clarke (1975)	£6·50 (Members £4·75) †
No.13	*The pathogenisis of reflux nephropathy (Chronic atrophic pyelonephritis),* by C. J. Hodson, T. M. J. Maling, P. J. McManamon and M. G. Lewis	£1·90 (Membership £1·75)

*Also special price to members of the Hospital Physicist's Association
†Also special price for individual users, 1 copy only

The British Journal of Radiology (1978) Supplement No.14

Reflux and Renal Scarring

by P. G. Ransley, M.A., M.B., F.R.C.S. and R. A. Risdon, M.D., M.R.C.Path.

Professor C. J. Hodson and his colleagues have shown the essential link in the association of chronic pyelonephritis with vesico-ureteric reflux: renal scarring in the growing kidney is related to intrarenal reflux of urine ("The Pathogenesis of Reflux Nephropathy", British Journal of Radiology Supplement No. 13, 1975). These ideas have now been taken further by Ransley and Risdon, again using the growing kidney of the infant pig. Their starting point is the morphology of the renal papilla. The different shapes of papillae, determined by the lobar structure of the kidney, are critical to the occurrence of intrarenal reflux.

These meticulous experimental studies answer many of the questions which have beset this subject: what are the pressure relationships of intrarenal reflux, why does scarring occur at predictable sites within the kidney, what are the mechanisms of progressive pyelonephritic deformity?

The authors have carried out carefully controlled experiments to test the importance of infection to renal scarring. Does sterile intrarenal reflux alone lead to scarring? Ransley and Risdon show that infection is an essential component to the initiation of the renal scar.

This work has far-reaching practical implications for understanding chronic pyelonephritis, and therefore for its medical/surgical management. Paediatricians, nephrologists, urologists, radiologists and all who care for children with urinary infection will read it with interest.

PRICE: £3·60 (Members of The British Institute of Radiology £3·00)

ORDER FORM

Reflux and Renal Scarring

PRICE: £3·60 (B.I.R. Members £3·00)

Post to:
The British Institute of Radiology,
32 Welbeck Street,
London W1M 7PG

Please supply copies

Cheque/postal order for £ enclosed (pounds sterling)

Dispatch to:

Name

Address

Signature

(Other Supplements still available are listed overleaf)

1978, *British Journal of Radiology*, *51*, 481–483

VOLUME 51 NUMBER 607 JULY 1978

The British Journal of Radiology

Continental notebook

Review of the continental radiological literature

By W. A. Fuchs, M.D.

Department of Diagnostic Radiology, University Hospital, Bern, Switzerland

This notebook covers the years 1976/77. Instead of being restricted to a review of German radiological literature it now includes a survey of selected French publications. Italian and Spanish papers will be introduced in future continental notebooks.

The two main French radiological journals are *Journal de radiologie, d'électrologie et de médecine nucléaire* and *Annales de Radiologie*. The first, now in its 58th year, is the official bulletin of the French Society of Radiology, and publishes the scientific programmes and reports of the society, covering both diagnostic and therapeutic aspects of radiology. The junior journal, *Annales de Radiologie*, 20 years of age, contains mainly radiodiagnostic publications, and regularly reports the proceedings of the European Society of Paediatric Radiology and recently of the European Society of Cardiovascular Radiology. Both journals print comprehensive summaries in English (the bibliography usually includes the Anglo-Saxon literature), and the technical quality of the reproduction of radiographs is generally good. A new trend in German radiology is worth mentioning. Some excellent articles by non-German authors are being printed in English, thus breaking the language barrier and opening up the papers to an international audience.

Radiology at War[1] is one such publication in English of wide interest, giving, as it does, an account of the role of radiology in the 1973 Yom Kippur War at a medical hospital centre in Israel. Radiology was essential in diagnosis and became the vital link in casualty flow. Eighty per cent of the wounded were sent immediately from the triage area to the radiology department. Traumatic injuries to the extremities were seen in 40%. Radiological problems were mainly confined to localization of metallic splinters with multiple radiographs, whereas fluoroscopy was thought to be time-consuming and therefore inadvisable.

"Angiography" still occupies a prominent place in all continental radiological journals. The 200 pages of proceedings of the first congress of the European Society of Cardiovascular Radiology[2] included the following subjects: automatic contrast agent injectors, fibromuscular dysplasia of the renal artery, and obstructive myocardiopathy. Many of these papers are well worth reading. Three publications in English by the group of Roesch cover extensively the subject of angiography in liver disease. Infusion hepatic angiography (36–60 ml in 4 sec) improves the diagnostic accuracy of the capillary phase.[3] Angiographic diagnosis in major hepatic processes[4] was incorrect or not satisfactory in 6% of 183 cases; suppurative hepatocarcinoma and liver cyst, retronodular regenerative cirrhosis and multiple intrahepatic abscesses were among the diagnoses missed. Angiography in the diagnosis of liver disease in 64 children was thought to be particularly useful in diagnosis and for planning the surgical management of liver masses.[5] The indications for angiography in liver masses have certainly changed very recently, due to the advent of ultrasonography, CT-scanning and, particularly, guided fine needle biopsy. All these papers are valuable if one considers that angiography is mainly indicated for pre-operative planning. The same also applies to pancreatic angiography, with the exception perhaps of endocrine active tumours of the pancreas. These are usually highly vascularized and therefore well demonstrated by angiography, as presented in a review of the literature (262 cases).[6]

Angiographic management of gastro-intestinal bleeding is covered in two excellent survey articles in English by the Boston and Oregon groups.[7,8] Intra-arterial infusion of vasopressin has been successful in treating gastric mucosal haemorrhage in 80%, gastric ulcers in 70% and acute colonorectal bleeding, mainly left flexure from diverticula, in about 90%.[7] Selective transcatheter embolic occlusion is also applied to control arterial bleeding, and seems to offer promising means for the management of haemorrhage from gastro-oesophageal varices.[8]

Two papers on angiography of the hand deserve special mention. Angiography of a traumatized hand was performed in 150 cases under plexus anaesthesia and with magnification technique.[9] Angiography is said to be indispensable when secondary surgery is planned and for post-operative control, because the possibilities of the healing of surgical repairs entirely depend on the degree of vascularity. Post-reserpine pharmacodynamic angiographic studies in combination with angiography after cold exposure were demonstrated to be a useful technique in 48 patients with Raynaud's syndrome, both diagnostically and in predicting the outcome of vasodilator therapy.[10]

Venography of parenchymatous visceral organs has recently gained increasing attention. Temporary venous occlusions by means of a balloon catheter produce excellent visualization of the venous system.[11] In the reviewer's opinion and experience catheter venography of the parenchymatous visceral organs has limited practical indications—mainly to demonstrate operative spleno-renal shunts, obstruction of the hepatic veins and malignant invasion of the renal vein.

A modification of Dotter's transluminal recanalization by means of a catheter with a dilatable cover[12] has proved to be a substantial technical improvement. The catheter has a double lumen, one to accommodate contrast medium, a guide wire or stiff cannula, the second for filling the expansible segment. The favourable therapeutic results published compare well with the reviewer's own smaller series.

Whole body computer tomography is making progress on the Continent with the appearance of new continental made fast CT scanners by Siemens and Philips. Several working groups in Belgium,[13] France[14] and Germany[15,16] have published accounts of their early experience with first and second generation CT equipment. Furthermore, a well attended international symposium was held in Heidelberg in October 1977. Practical results obtained with fast CT scanners based upon prospective comparative clinical-radiological studies must, however, be awaited before conclusive statements on the actual value of this exciting new method can be made. This is particularly true when considering the good results of grey-scale ultrasonography. Two excellent articles on the normal vascular anatomy of the abdomen deserve mention,[17,18] since the abdominal vascular structures are important landmarks for diagnosis and localization of pathologic abdominal lesions. Two well illustrated and well documented volumes on abdominal grey-scale ultrasonography were published in German in 1977.[19,20] Both books contain an interesting and vast iconography but fail to integrate the method into the total context of diagnostic radiology. In the reviewer's opinion all imaging methods, *viz.* conventional radiography, angiography, nuclear medicine, ultrasonography and CT-scanning, must be regarded as one entity. A comprehensive analysis of the clinical value of ultrasonography within the context of diagnostic radiology as a whole is, therefore, still awaited.

The great majority of publications still deal with conventional diagnostic radiology. Many of them are small stones in the progressively larger building of diagnostic radiology, but many also consist mainly of repetitions and "déja-vu" experiences. In the reviewer's personal view the following observations deserve special mention. Changes in pulmonary blood flow patterns and loss of marginal definition of basal pulmonary vessels are unreliable signs of left heart insufficiency in old and non-co-operative patients, and in the presence of elevated diaphragm.[21] The emergency erect plain film of the abdomen used to detect a pneumoperitoneum should be taken in expiration.[22] An excellent comprehensive overview is given on parasitic calcifications.[23] A multicentre enquiry in France of 100 cases of extrahepatic biliary lithiasis in children showed that congenital haemolytic anaemia was the cause in half of the cases, followed by hepatic disorders, biliary malformations and partial resection of the small intestine.[24]

The proceedings of the 1976 Stockholm meeting of the European Society of Paediatric Radiology are presented in the January 1977 number of *Annales de Radiologie*[25]. Most of the papers and abstracts are printed in English, some of which treat subjects of particular interest, such as: radiation dose to the eye lens, pulmonary abnormalities in immunosuppressed children, neonatal renovascular hypertension, tumours of the lower urinary tract in infants and children, hypophosphatasia (review of 24 cases) and a 20-year prospective follow-up of childhood hiatal hernia.

Looking critically through the French and German radiological journals, and bearing in mind the excellent contents of the two British journals and of the Scandinavian and Dutch journals (all printed in English), the reviewer gets the impression that the quality of European Radiology easily matches that of the North American continent. The diversity of the European national characters, which is also reflected in radiological science, may prove to be an additional stimulus, provided there is continuing co-operation under the aegis of such bodies as the European Radiological Society and the European Congress of Radiology. But politically engendered nationalistic reasoning must be completely eradicated.

LITERATURE

1. *Der Radiologe*, *17* (1977), 437.
2. *Annales de radiologie*, *20* (1977), No. 3–4.
3. *Fortschr. Röntgenstr.*, *124* (1976), 534.
4. *Fortschr. Röntgenstr.*, *127* (1977), 1.
5. *Radiologia clin.*, *46* (1977), 321.
6. *Radiologia clin.*, *46* (1977), 401.
7. *Fortschr. Röntgenstr.*, *127* (1977), 111.
8. *Fortschr. Röntgenstr.*, *125* (1976), 301.
9. *J. Radiol. Electrol.*, *58* (1977), 93.
10. *Fortschr. Röntgenstr.*, *127* (1977), 30.
11. *Fortschr. Röntgenstr.*, *127* (1977), 222.
12. *Fortschr. Röntgenstr.*, *124* (1976), 80.
13. *Fortschr. Röntgenstr.*, *126* (1977), 285.
14. *J. Radiol. Electrol.*, *58* (1977), 253.
15. *Fortschr. Röntgenstr.*, *127* (1977), 399.
16. *Fortschr. Röntgenstr.*, *127* (1977), 405.
17. *Fortschr. Röntgenstr.*, *127* (1977), 89.
18. *Annales de radiologie*, *20* (1977), 625.
19. KRATOCHWIL, A., 1977. *Ultraschalldiagnostik in der Inneren Medizin, Chirurgie und Urologie* (Georg Thieme Verlag, Stuttgart).
20. SCHNEEKLOTH, G., FRANK, TH., and ALBERS, G., 1977. *Ultraschalltomographie abdomineller Organe und der Schilddrüse im Grey-Scale-Bild* (Verlag Enke, Stuttgart).
21. *Fortschr. Röntgenstr.*, *125* (1976), 325.
22. *J. Radiol. Electrol.*, *58* (1977), 171.
23. *J. Radiol. Electrol.*, *58* (1977), 125.
24. *Annales de radiologie*, *19* (1976), 487.
25. *Annales de radiologie*, *20* (1977), No. 1.

Book review

The Hospital Preparation of Radiopharmaceuticals, HPA Scientific Report No. 16, 1977. pp. 47, £3·00.

This scientific report deals with the preparation of radiopharmaceuticals incorporating short-lived radio-nuclides such as $^{99}Tc^{m}$ and $^{113}In^{m}$, and was prepared by members of the HPA radionuclide topic group and a pharmacist experienced in the quality control of these agents. The working conditions and procedures in hospital radiopharmaceutical laboratories have altered considerably since the change took place from long-lived to short-lived radiopharmaceuticals, and there is an increasing awareness of the need to prepare parenteral diagnostic radiopharmaceuticals under properly controlled conditions. Such changes have made the physicist or pharmacist concern himself more closely with the details and methodology of small-scale manufacturing and quality assurance of radiopharmaceuticals.

This report gives much useful guidance to all concerned in the manufacture of radioactive diagnostic agents. It consists of four main sections dealing with the preparation, analytical control, reliable methods and procedures, and a summary of commercially available radiopharmaceutical kits.

The section on preparation of radiopharmaceuticals contains a great deal of useful and practical information on the facilities and equipment needed for this purpose, although the preliminary description of sterilization methods is far too sketchy to be of any practical value. Aseptic dispensing of thermolabile materials (which cannot be heat sterlized, and comprise the majority of commonly used radiopharmaceuticals) in properly controlled aseptic areas is described in some detail and provides a useful summary of methods and techniques which must be employed with radioactive materials.

Analytical testing of hospital manufactured radiopharmaceuticals should always be regarded as part of the manufacturing process even though some of the tests must be retrospective. The section on analytical testing gives general standards for radioactivity, radionuclidic and chemical purities, and some cautionary information on radiochemical purity determination by chromatography, but no recommendations are made on specific systems for checking radiochemical purities of diagnostic agents prepared from hospital or commercial kits. A table showing a few of the more reliable systems would have been helpful. Standards for injections are discussed in terms of their sterility, apyrogenicity, and particulate contamination. Successful sterility testing procedures depend largely on the sampling scheme adopted; with the small batch sizes encountered in radiopharmaceutical manufacture it is doubtful whether much useful information can be obtained. The report recognises this difficulty and recommends regular production of simulated injections using sterile microbial growth media to supply meaningful data. Microbial contamination checks on production facilities are described in the preceding section, but a summary of these would have been useful at this point.

The fourth section gives 13 methods for the preparation of eight frequently used radiopharmaceuticals (mainly $^{99}Tc^{m}$) which have been selected from a longer original list and tested in at least five laboratories. While the recipes themselves are very detailed, no information is given on the quality of the product obtained, a surprising omission in view of the emphasis placed on analytical testing. It is debatable whether the work involved in the development of in-house radiopharmaceutical kits can be justified when similar materials are available commercially.

The last section lists commercial radiopharmaceutical kits available in the UK in April 1976 and summarizes the main features of each kit under manufacturer headings. Such lists can never be completely up to date and in the radiopharmaceutical area new kits are introduced and existing ones are reformulated at a rapid rate. One solution to this problem is to maintain a file of current manufacturers' product literature in individual establishments and to draw up local lists and summaries, and the lists published in this report form a basis for such activities.

On the whole this report gives some very useful advice and guidance on the commissioning and running of a hospital radiopharmacy and should be essential reading for all those engaged in the preparation and use of radiopharmaceuticals in hospitals.

A. E. THEOBALD.

1978, *British Journal of Radiology*, *51*, 484–493

Abdominal contrast tomography in the evaluation of the gall-bladder and biliary tract (with emphasis upon jaundiced patients)

By L. Dalla Palma, M. Bazzocchi, and M. di Pietrantonio

Departments of Diagnostic Radiology and Surgery, University Hospital, Trieste, Italy

(*Received March, 1977 and in revised form January, 1978*)

ABSTRACT

Tomography of the right upper quadrant after the rapid intravenous infusion of a high dose of contrast medium is a valuable method of investigation of hepato-biliary disease. Gall-bladder wall opacification may be normal, but if the wall is thicker than 2 mm and if irregular, it indicates inflammatory or calculous disease. Gall-bladder area greater than 35 cm² indicates bile duct obstruction. This also causes the ducts to appear as lucent bands within the opacified liver parenchyma. Secondary deposits in the liver may also become visible. Various patterns of these findings are described which suggest specific biliary abnormalities.

We have recently published a preliminary report on the evaluation of the liver using abdominal contrast tomography (Dalla Palma *et al.*, 1977). Genereux and Tchang (1970a and b) were the first to visualize

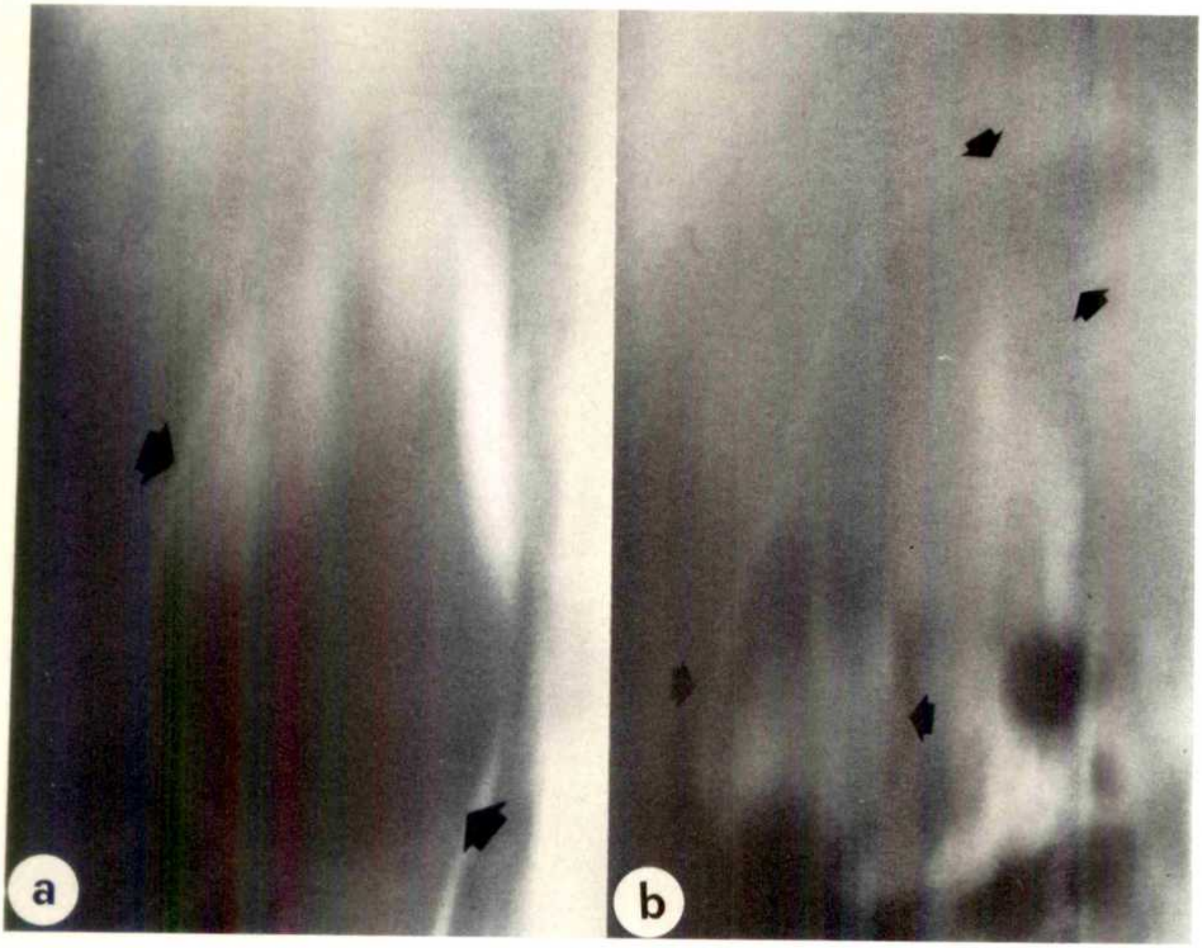


FIG. 1.

(a) Dilated gall-bladder: the wall is thin medially and thickened laterally (female, 27: chronic cholecystopathy with stones, right upper quadrant mass).

(b) Long gall-bladder: the wall is thickened laterally (female, 55: chronic cholecystopathy with stones).

the wall of the gall-bladder in obstructive chronic cholecystopathy during total body opacification induced with high dose infusion; Rabuschka *et al.* (1973) confirmed their results. Lately Love (1976) has pointed out the value of this technique in patients with acute cholecystitis, while Dalla Palma (1977) and Morin *et al.* (1976) have demonstrated dilated bile ducts in jaundiced patients. We again wish to emphasize the value of this simple technique for the study of the non-visualized gall-bladder and for differentiating obstructive from non-obstructive jaundice.

MATERIAL AND METHOD

Technique

The technique is based on a rapid intravenous infusion (100–120 ml/min) of 150 ml Conray 400, equal to 60 gm of iodine, diluted in the same volume of 5% dextrose. At the end of the infusion linear tomography is performed of the right upper quadrant of the supine patient; the tomographic angle is 40 deg.; tomograms are taken every centimetre for a total of ten starting at 3 cm from the anterior abdominal wall. Tomography is repeated 15 minutes later in cases where the gall-bladder wall does not opacify.

Clinical material

Controls. Control studies of the visualization of the normal gall-bladder wall were obtained by tomographing the right upper quadrant of 98 patients undergoing nephrotomography; these patients were examined 15 minutes after infusion of contrast.

Non-visualized gall-bladder. We have examined 61 patients with non-visualized gall-bladders at cholecystography and cholangiography; their history suggested gall-stones, some had right upper quadrant masses. Our purpose was to visualize the gall-bladder wall so as to assess its thickness and to measure the size of the organ. Twenty-three of these patients underwent cholecystectomy and pathological studies of the wall were performed in all cases.

Suspected obstructive jaundice. We have also considered a group of 47 patients with jaundice of five to 60 days' duration: in such cases we looked for dilated intrahepatic ducts; we also determined gall-bladder size through the visualization of the opacified wall.

The importance of demonstrating the liver as well as the gall-bladder led us to modify our technique in these cases, increasing kVp by four and obtaining tomograms as far back as 6–8 cm from the posterior abdominal wall. A correct exposure is essential when examining the liver because the lucency of the dilated

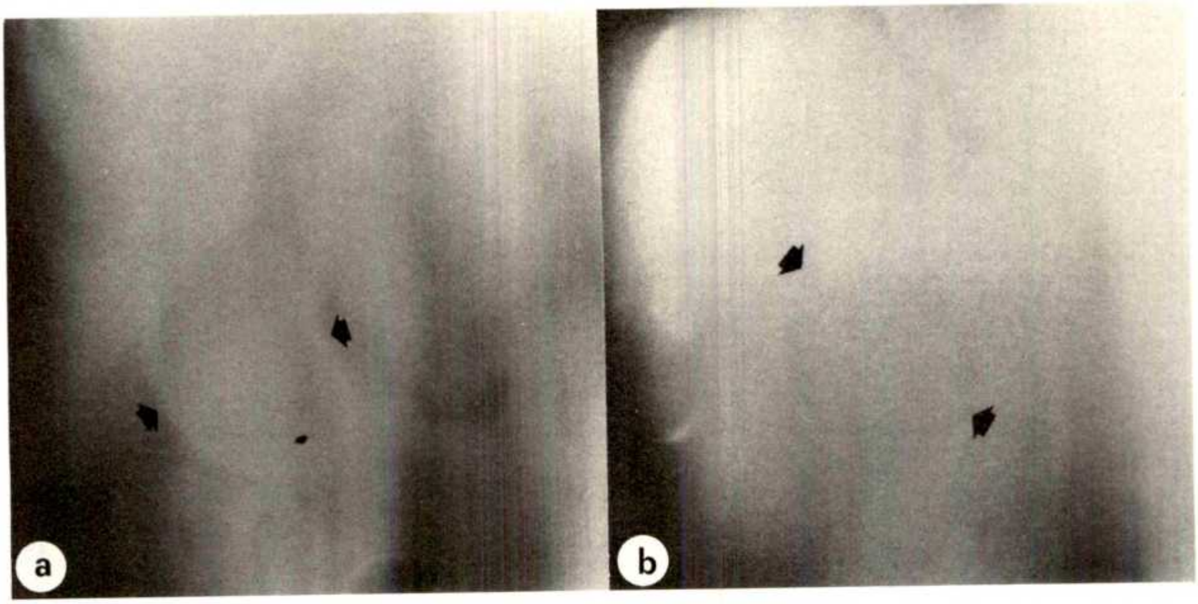


FIG. 2.

(a) Small gall-bladder: the wall is thinned toward the fundus (small arrow) site of a stone decubitus (female, 52, with chronic cholecystopathy and stones).

(b) A gall-bladder with a thin wall, scarcely visible because embedded in the liver (female, 64, with chronic cholecystopathy and stones).

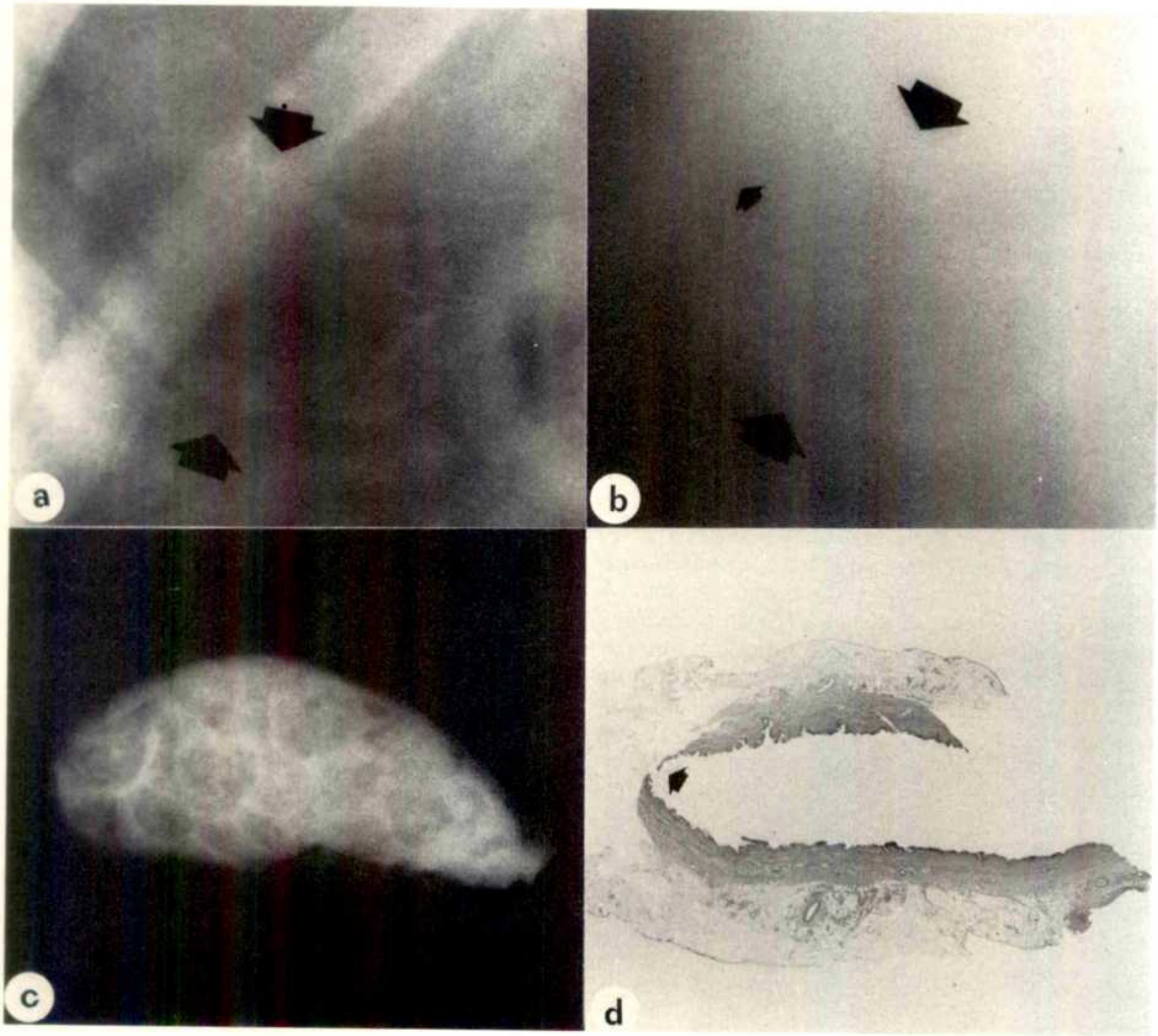


Fig. 3.

Chronic cholecystopathy in a 66-year-old woman. The radiograph right after infusion shows: (a) the entire wall with variable thickness; the wall is thin right above the fundus (small arrow) because of stone pressure, which is well demonstrated on the radiograph of the specimen (c) and on the microscopic section (d). Tomography shows the wall only partially (b).

biliary tract is very faint and may be overlooked on under-exposed films. They may be visualized only during the first five minutes following infusion; a wrong exposure cannot be corrected in the second series of tomograms as liver opacification rapidly declines.

Of this third group we have considered only the 42 patients who underwent surgery, biopsy or autopsy. The final diagnosis in these cases included pancreatic carcinoma (10), gall-bladder carcinoma (5), bile duct carcinoma (4), ampullary or peri-ampullary carcinoma (2), primary carcinoma of liver (2), metastatic carcinoma (5), chronic pancreatitis (1), common bile duct stones (10), sclerosing cholangitis (1) and cirrhosis with intrahepatic cholestasis (2).

Results

Control studies

Of the 98 patients studied, 41 showed opacification of the gall-bladder wall, a much higher incidence than that shown by Genereux and Tchang (1970a, b) or Rabuschka *et al.* (1973), probably because of the higher dose rate.

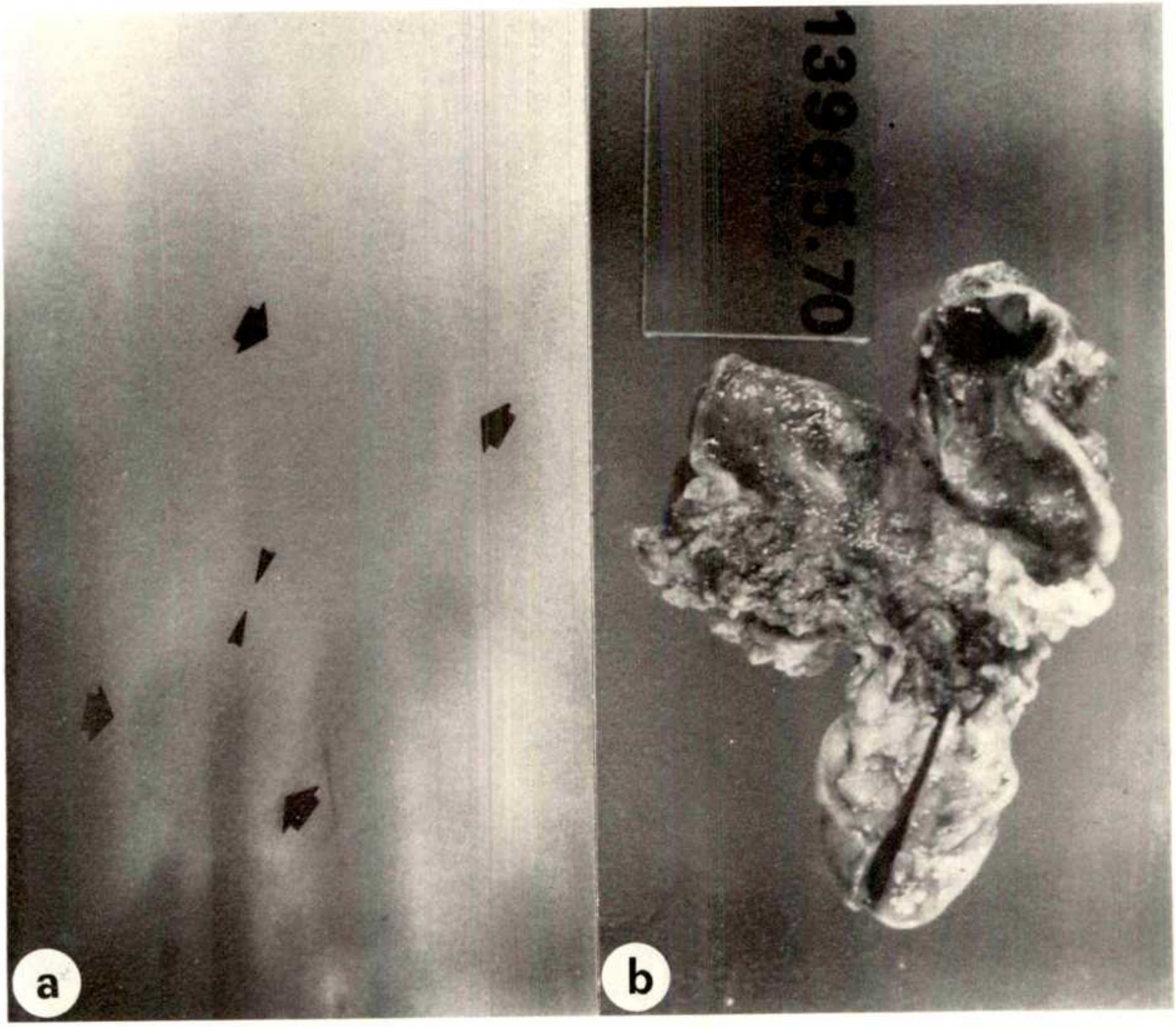


FIG. 4.

Chronic cholecystopathy with stones in a 55-year-old woman.

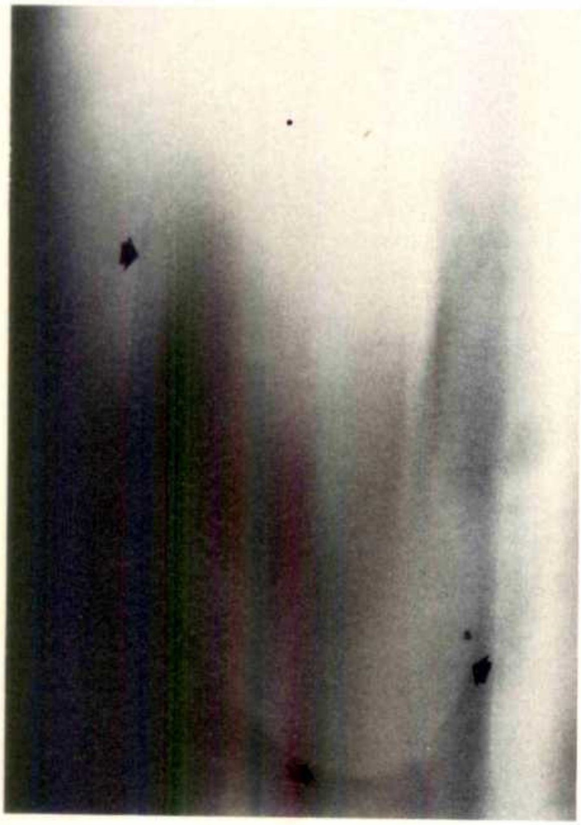
(a) Abdominal contrast tomography shows a thick irregular wall with a transverse septum.

(b) The surgical specimen.

In order to see if wall opacification in control cases might indicate an abnormal gall-bladder, we performed oral cholecystography in 18 patients with wall visualization and in ten without opacification of the wall. The first group showed faint gall-bladder opacification in three, gall stones in three, adenomyomatosis (cholecystosis) in one and non-visualization in two cases; the non-visualization was confirmed by intravenous cholangiography. It is of particular interest that six of these nine patients showed an irregularly thickened wall on contrast tomography while all patients with normal cholecystography showed a thin wall. Of the ten patients in the second group, the gall-bladder visualized normally in nine cases. These observations suggest that opacification of a thickened wall on contrast tomography indicates inflammatory or calculous gall-bladder disease. On the contrary, the opacification of a thin wall, less than 2 mm, has an uncertain meaning as it may be seen even in normal gall-bladders.

The non-visualized gall-bladder

In the group of 61 patients with non-visualization of the gall-bladder, at both oral and intravenous examination, the gall-bladder wall was opacified in 55 (90%). We shall consider only the 23 cases in



whom surgery provided pathological confirmation of the radiological findings. Nineteen had chronic cholecystitis with stones, three had calculous disease with empyema of the gall-bladder and one had pancreatic cancer with a hydropic gall-bladder.

All these cases showed wall opacification: it was partial in two and virtually complete in the remainder, enabling us to measure the size of the gall-bladder. The length varied between 2 and 20 cm and the transverse diameter was 1.5 to 8 cm. Wall visualization was obtained not only in the distended and normal sized gall-bladders (Fig. 1) but also in the small, sclero-atrophic ones (Fig. 2). Small gall-bladders are poorly visualized when they are embedded in liver parenchyma because contrast differentiation is abolished (Fig. 2b). This was probably why the wall was not visualized in six of our cases, none of whom had surgical control.

When opacification occurs the gall-bladder wall is well shown in the early series of tomograms but visualization often improves after 15 minutes, presumably when the diffusion of contrast into the wall

FIG. 5.

Male, 73: right upper quadrant mass. At surgery: pancreatic cancer and hydropic gall-bladder. Contrast tomography shows an enormous gall-bladder, 20 cm long, with a thin wall.

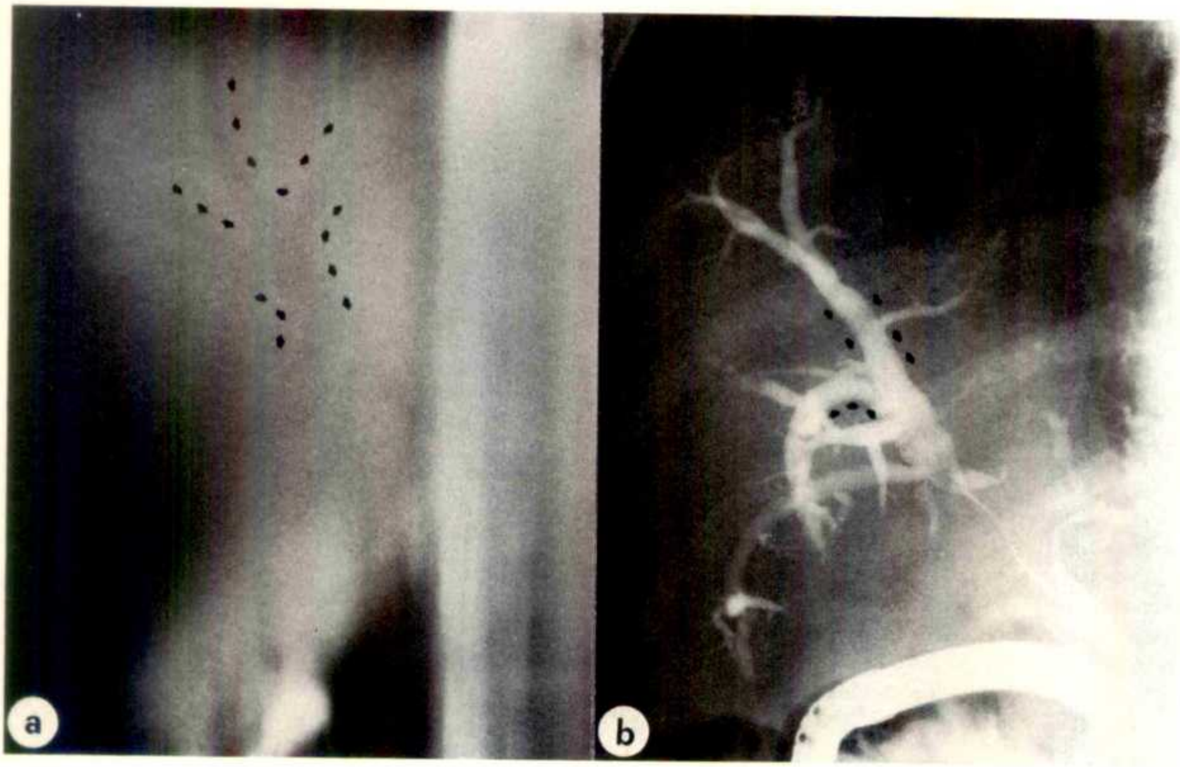


FIG. 6.

Female, 69; jaundice dating 30 days; metastatic carcinoma in porta hepatis. Contrast tomography shows: (a) right lobar negative cholangiogram, *i.e.* the lucency of the dilated hepatic ducts; more ducts are visualized by this technique than by endoscopic retrograde cholangiography (b).

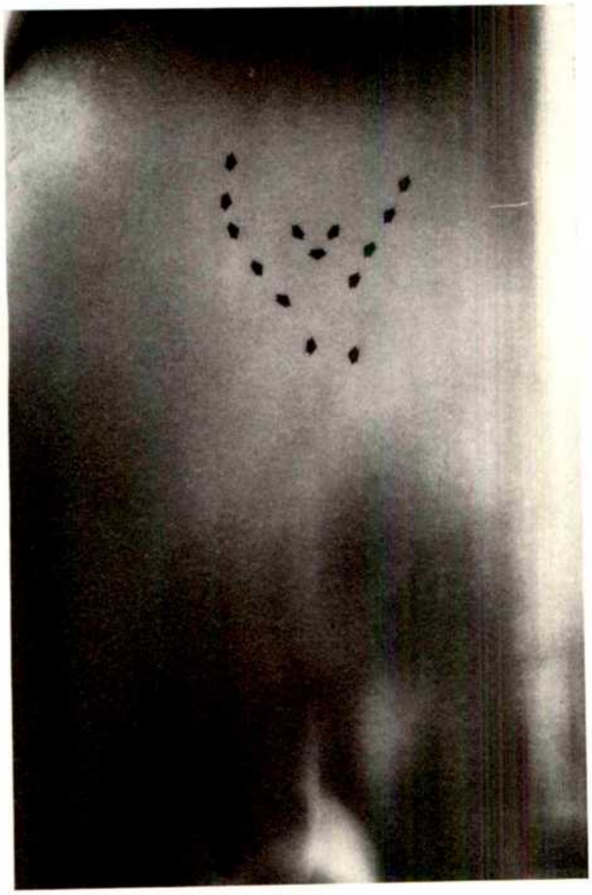


Fig. 7.

Female, 56, with jaundice dating 30 days; at surgery a stone was found in the common bile duct. Contrast tomography shows slight dilatation of the ducts in the central part of the liver (central negative cholangiogram).

is at its maximum. The entire wall is often seen on standard radiographs (Fig. 3a): on the other hand, in tomography of oblique or curved gall-bladders, only part of the wall may be seen (Fig. 3b) necessitating more tomograms. In most cases of disease the wall is not equally thick; it increases where fibrosis or oedema are present and is reduced when the mucosal or muscle layers are hypoplastic or atrophic.

In this group at surgery the wall thickness was between 1 and 5 mm; even some non-distended gall-bladders showed a very thin wall. In a few cases with stones and increased thickness, the internal wall showed indentations due to stone pressure; the indentations are well seen on the radiograph of the operated specimen (Fig. 3c) and on the microscopic section (Fig. 3d). When such indentations are recognizable, the diagnosis of calculous gall-bladder disease is possible. No difference was shown in the wall pattern between acute and chronic gall-bladder disease.

Jaundiced patients

The findings in these subjects may be considered under three headings—the negative cholangiogram, the visualization of the gall-bladder wall and opacification of the liver parenchyma.

Negative cholangiogram. This term has been used (Dalla Palma, 1977) to refer to the translucent image of the bile ducts in the opacified liver during total body contrast opacification. In some cases it is also possible to see part of the extrahepatic bile ducts, though the distal portion is usually masked by the vertebrae. The image here is faint, depending on wall opacification, on surrounding fat and the absence of nearby opaque structures; visibility improves with dilatation. Intrahepatic duct visualization depends on the region examined. With minor dilatation, ducts show faintly as lucent lines best seen at the periphery of the right lobe. The ducts of the left lobe, though more often dilated, are less well seen because of the lesser parenchymal thickness and because of "parasitic streaks" due to the vertebral column. The intrahepatic cholangiogram may be partial or almost complete (Figs. 6 and 7).

Forty-two cases were considered. The negative cholangiogram was seen in 31 of the 32 patients with obstruction of the extrahepatic ducts. No cholangiogram was seen in seven cases of primary or secondary liver carcinoma nor in the two cases of cirrhosis with intrahepatic cholestasis. The case of sclerosing cholangitis with jaundice of 30 days' duration showed only a faint intrahepatic negative cholangiogram. Cases with duct stones showed only slightly dilated ducts (Fig. 6). In the remaining cases, dilatation was usually marked (Fig. 7) and sometimes really striking as in pancreatic or peri-ampullary carcinoma (Fig. 8). The maximum calibre of intrahepatic ducts was 23 mm.

An extrahepatic cholangiogram was seen in 19 of the 32 patients with extrahepatic obstruction; the calibre varied from 10 to 32 mm (Table I). Dilatation of the extrahepatic ducts was most frequent in neoplastic stenoses of the lower bile duct, usually of at least 30 days' duration (Figs. 8 and 9).

Gall-bladder wall opacification. The gall-bladder was seen in 23 of 29 patients with obstructed extrahepatic ducts and intact gall-bladders. We measured the gall-bladder area, which varied from 8 to 66 cm^2; like Redman and Reuter (1970) we considered those with an area greater than 35 cm^2 to be enlarged. Gall-bladder size varied with underlying disease (Table I).

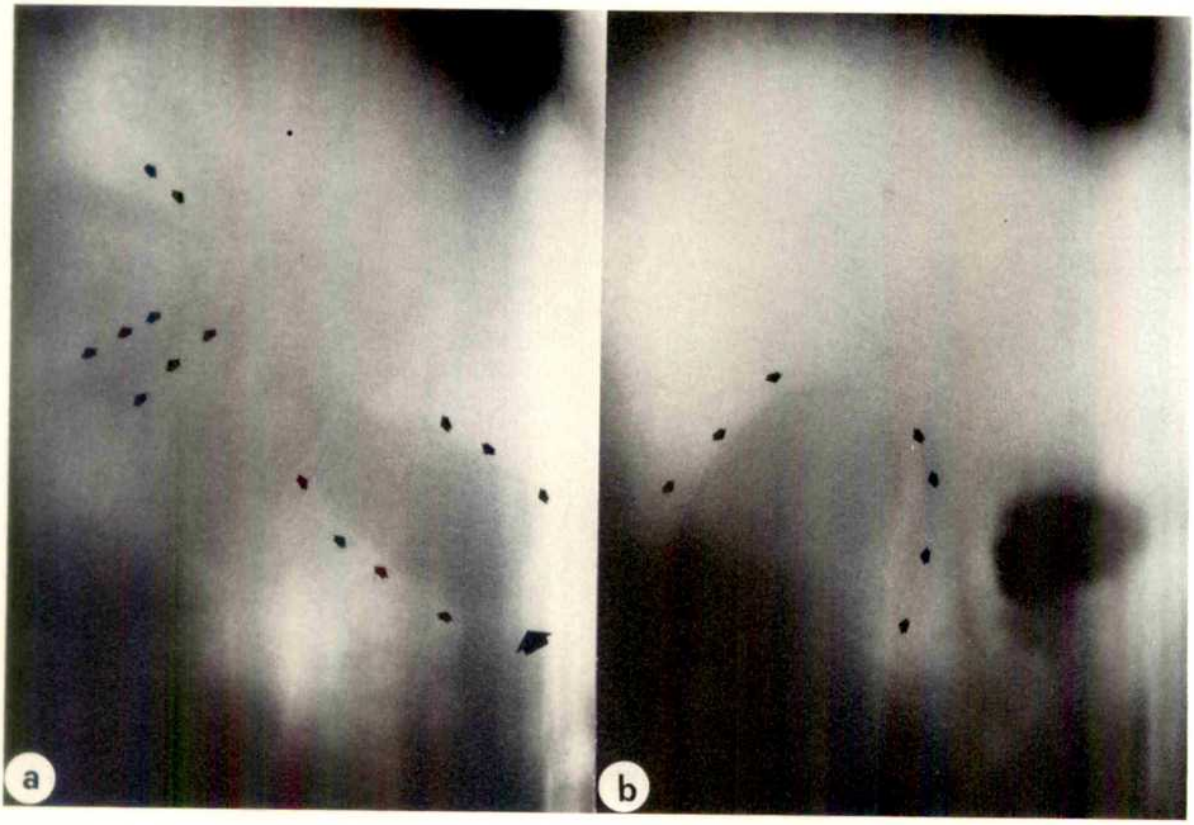


Fig. 8.

Male, 60, with jaundice for 45 days: at surgery a peri-ampullary carcinoma and an hydropic gall-bladder were found. Contrast tomography shows enormous dilatation of the biliary ducts and of the common bile duct (a); hydropic gall-bladder with a thickened wall (b).

TABLE I

Radiological findings in extrahepatic obstructive jaundice observed in 32 cases with abdominal contrast tomography

Diagnosis	Number	Intrahepatic ducts visibility			Extrahepatic ducts calibre, mm			Gall-bladder	
		Good ++	Poor +	Number visualized	Min.	Max.	Number visualized	wall area, cm^2	Number visualized
Ca gall-bladder	5	5		5/5	15	20	3/5	17	5/5
Ca biliary ducts	4 (1)	4		4/4		30	1/4		0/3
Peri-ampullary Ca	2	2		2/2		30	2/2	38.5	2/2
Common duct stones	10 (2)	3	7	10/10	10	20	4/10	19	5/8
Ca pancreas	10	8	1	9/10	12	32	8/10	41.5	10/10
Chronic pancreatitis	1	1		1/1		20	1/1	47	1/1
Totals	32 (3)			31/32			19/32		23/29

Figures in brackets ( ) indicate patients who underwent cholecystectomy before examination.

The wall did not opacify in three cases of extrahepatic duct carcinoma nor in three cases of duct stones. The remaining cases of duct stones showed normal thickness and area. The five cases of gall-bladder cancer showed irregular wall thickening and a reduced area (Fig. 10), while distal duct stenosis caused gall-bladder distension with thinning of the wall.

Our only case of chronic inflammation of the gall-bladder showed an irregular thickened wall with an area of 14 cm². In spite of the suspicion of gall-bladder cancer, pathological examination showed only chronic inflammatory change.

These findings give rise to characteristic patterns in the common causes of obstructive jaundice as follows (Table I): distal obstruction of the bile duct (carcinoma of pancreas, ampulla or distal bile duct, chronic pancreatitis) show marked intrahepatic and common bile duct dilatation (up to 30 mm), with an enlarged gall-bladder (Figs. 8 and 9). In duct stones the negative cholangiogram is faint (Fig. 7), with moderate bile duct dilatation; the gall-bladder is normal or small, often with a thickened wall. Carcinoma of common and hepatic duct or upper bile duct (Fig. 6) show a negative cholangiogram with marked duct dilatation; the gall-bladder when seen is small.

Gall-bladder carcinoma involving the common bile duct (Fig. 10) shows pronounced intrahepatic duct dilatation; the gall-bladder wall is always shown and is irregularly thickened; sometimes with enlarged tortuous veins around the fundus.

Liver parenchyma opacification. This is of value not only for showing dilated ducts but in demonstrating some cases of primary or metastatic liver cancer which may be visible because of a poor or an increased blood supply (Dalla Palma *et al.*, 1977). Occasionally it is difficult to distinguish metastatic lucencies from dilated ducts seen end-on: large peripheral lucencies suggest metastases.

Liver infiltration occurs frequently in gall-bladder cancer. It gives rise to a lucent area, sometimes very

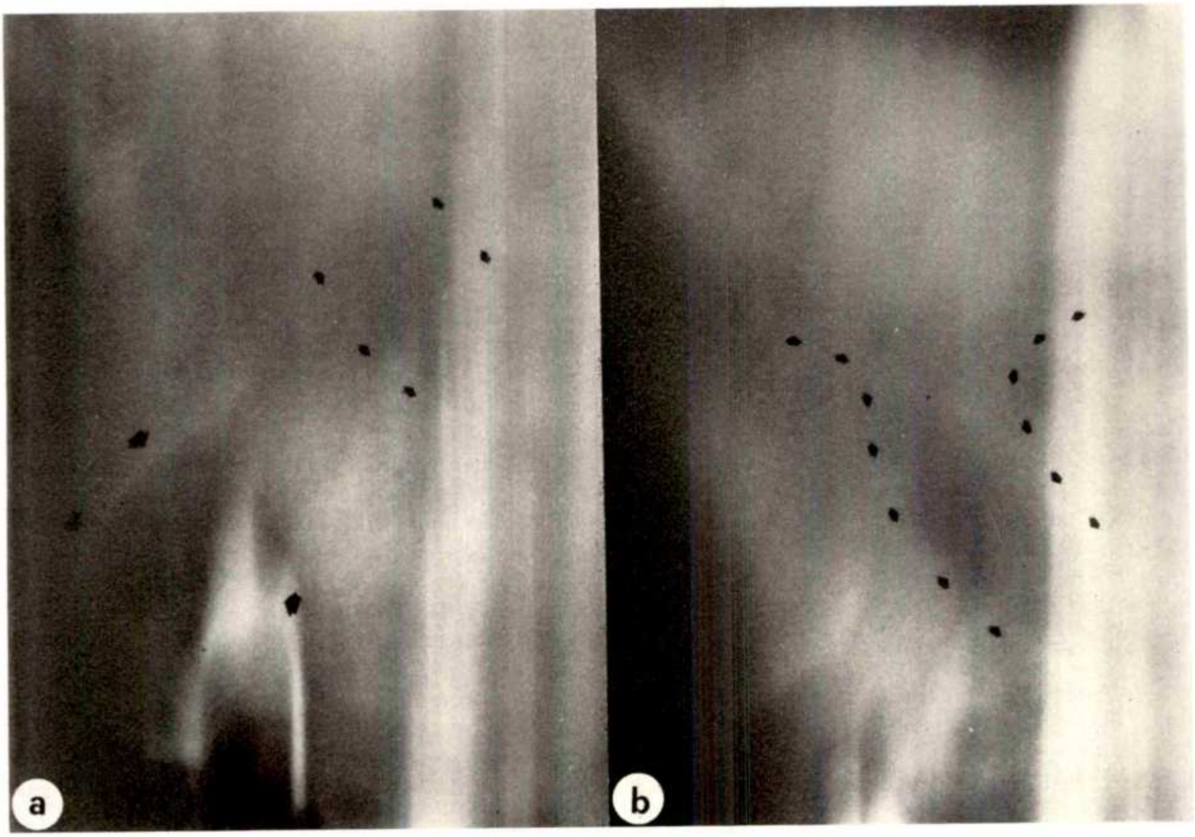


FIG. 9.

Female, 43, with jaundice dating 45 days: peri-ampullary carcinoma at surgery. Contrast tomography (a), (b) shows dilatation of the common bile duct, of the common hepatic duct, of the two hepatic ducts and the gall-bladder.

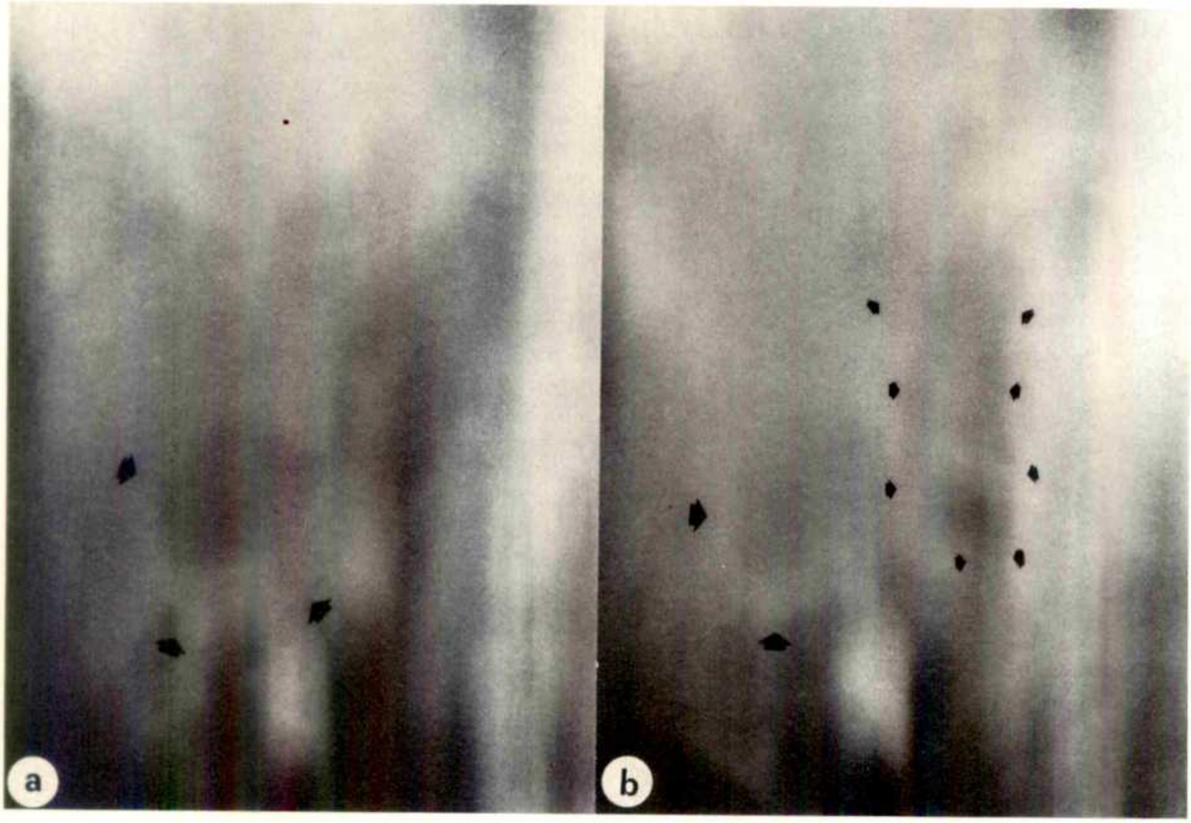


FIG. 10.

Female, 68, with jaundice dating five days: gall-bladder carcinoma at surgery. Contrast tomography shows: (a) a small gall-bladder, with very thick wall (arrows) and (b) the dilated hepatic duct (small arrows).

large, around the gall-bladder wall: this lucent area allows differentiation between carcinoma and chronic inflammation which also causes thickening of the gall-bladder.

Side effects

The procedure is well tolerated: like Davidson *et al.* (1970) and Milman and Stage (1974) we have found no adverse effects from the large doses of contrast. Estimation of SGPT and alkaline phosphatase before and after the examination showed no significant changes.

DISCUSSION

The indications for abdominal contrast tomography are:

Non-visualized gall-bladder. The size of the gall-bladder, the thickness and regularity of its wall are important. Wall opacification does not necessarily mean gall-bladder disease because a wall with thickness of less than 2 mm can be observed both in cases with gall-bladder disease as well as in normal or at least asymptomatic patients. Inflammation of the gall-bladder can be diagnosed only when wall thickness is more than 2 mm and irregular; the gall-bladder is considered enlarged when its area is more than 35 cm^2.

Presumed obstructive jaundice. The site and nature of the obstructing lesion can often be inferred by noting the degree of dilatation in the intrahepatic negative cholangiogram, the presence of extrahepatic duct dilatation and the size of the gall-bladder.

The technique is applicable at all levels of serum bilirubin. It is simpler and more accurate than arteriography which was suggested by Sprayregen and Messinger (1974) and can be used in departments without ultrasound facilities.

At a time when some workers are suggesting the use of computerized tomographic scanning for differentiating obstructive from non-obstructive jaundice (Alfidi, 1976) we would point out that the simple and relatively inexpensive technique of abdominal contrast tomography will do this in the great majority of cases.

REFERENCES

Alfidi, R. J., 1976. Computerized tomography of the gall bladder and biliary tract. *Seminars in Roentgenology*, *11*, 143.

Dalla Palma, L., 1977. Abdominal contrast-tomography. Its appraisal in the study of upper abdomen. (Proceedings of the Symposium Actualitatis Tomographie, Genoa, September 1975.) *Excerpta Medica, International Congress Series No. 392.*

Dalla-Palma, L., Bacarini, L., Bazzocchi, M., and Di Pietrantonio, M., 1977. The use of abdominal contrast-tomography in liver disease. *British Journal of Radiology*, *50*, 483–488.

Davidson, A. J., Becker, J. A., Rothfield, N., Unger, G., and Plock, D. R., 1970. An evaluation of the effect of high-dose urography on previously impaired renal and hepatic function in man. *Radiology*, *97*, 249–254.

Genereux, G. P., and Tchang, S. P. K., 1970a. Hydrops of the gall bladder: unusual roentgenographic demonstration. *Journal of the Canadian Association of Radiologists*, *21*, 39–42.

1970b. Diatrizoate—induced total body opacification in the diagnosis of obstructive cholecystopathy. *Journal of the Canadian Association of Radiologists*, *21*, 242–250.

Love, L., 1976. Infusion tomography of the gall bladder. *Seminars in Roentgenology*, *11*, 181–184.

Milman, N., and Stage, P., 1974. High dose in advanced renal failure. II. Influence on renal and hepatic function. *Acta Radiologica Diagnosis*, *15*, 104–112.

Morin, M. E., Baker, D. A., and Marsan, R. E., 1976. Demonstration of dilated biliary ducts by total body opacification. *Radiology*, *121*, 307–309.

Rabushka, S. E., Love, L., and Moncada, R., 1973. Infusion tomography of the gall bladder. *Radiology*, *109*, 549–522.

Redman, H. C., and Reuter, S. R., 1970. The angiographic evaluation of gall bladder dilatation. *Radiology*, *97*, 367–370.

Sprayregen, S., and Messinger, N. H., 1974. Angiography of the jaundiced patient with emphasis upon the angiographic appearance of biliary duct dilatation. *American Journal of Roentgenology*, *122*, 335–355.

Book review

Radiology of the Liver. By J. G. McNulty. Vol. 13. Saunders Monographs in Clinical Radiology, pp. xiii + 437, illus., 1977 (W. B. Saunders Company, USA) £22·00.

Radiology of the liver by James G. McNulty is the 13th in the series of Saunders Monographs in Clinical Radiology. To say that this is well up to the standard of its predecessors is praise indeed. Moreover, it claims to be the first comprehensive treatise on hepatic radiology in the English language.

There is a short introductory chapter on the microscopic and macroscopic anatomy of the liver with a detailed description of the variations commonly found in the vascular anatomy in health and disease. The portal venous system with various forms of porto-systemic anastomoses is well illustrated. The importance of an undertsanding of the peritoneal relations of the liver is discussed.

The largest single chapter is concerned with the individual techniques available for the investigation of liver disease. This covers all forms of conventional radiology, including angiography of all types, ultrasound examinations, computerized tomography and isotope studies. This is a particularly useful section of the book since it deals in some detail with the indications and limitations of each of the techniques described. Although the descriptions are quite brief, reference is given to important papers where further details can be obtained. This same brevity tends to favour the use of lists and a rather 'black and white style' of writing since it is not possible in the space available to go into sufficient detail to illustrate all the nuances of differential diagnosis. Even so the style is admirably clear so that the reader is never in any doubt as to the meaning of what has been written.

Other chapters cover a variety of conditions including hereditary and congenital disorders of the liver, trauma, inflammatory disorders, primary vascular disorders and tumours. In each of these the rôle of the different types of investigation is discussed. It would be helpful if it were possible to include some diagrams to indicate the optimum sequence of investigations, and the way in which the result of one examination would influence the choice of the next. Finally, there is a section on the radiology of systemic manifestations of liver disease in which such conditions as the arthropathy of haemochromatosis and the association between polycystic disease of the kidneys and focal dilatation of the hepatic bile ducts is discussed.

This is an extremely valuable book in that it brings together the whole gamut of the radiological investigations of the liver. It is well illustrated and each section is followed by a short bibliography. This is a very rapidly expanding field and the author is to be congratulated on incorporating many of the more recent advances. This book will find its place along with the other Monographs in this Series as a book of interest to many people. The radiologist in training will see it as a source of factual information for his professional examinations, more experienced radiologists will find much in it of great interest and a useful book for reference in case of doubt, and the physician and surgeon specializing in gastro-enterology will find that it gives him a bird's eye view of the available forms of radiological investigation in diseases of the liver.

J. W. Laws.

1978, *British Journal of Radiology*, *51*, 494–497

Subpulmonary pneumothorax

By A. Schulman, M.R.C.P., F.R.C.R., and R. B. Dalrymple, M.B., Ch.B., D.M.R.D., F.F.RAD(D) (S.A.)

Departments of Radiology, Groote Schuur Hospital and University of Cape Town, South Africa

(*Received October, 1977 and in revised form February, 1978*)

ABSTRACT

Seven cases of subpulmonary pneumothorax are presented: four due to penetrating injury, two to blunt trauma and one to osteosarcoma metastasis.

The typical and diagnostic appearance is a basal band of radiolucency bounded above by the thin hair-line of visceral pleura paralleling the dome of the hemi-diaphragm. When partially clotted blood is also present, the appearance becomes less typical and has to be differentiated from traumatic diaphragmatic herniation of bowel and from traumatic pneumatocoele by barium studies and by decubitus radiographs respectively.

It is the bridge-like disposition of the pleural cavity between the dome of the hemi-diaphragm and the hollowed concavity of the lung base which allows pneumothorax to collect in it. It is rarely seen because blebs and bullae which are the commonest causes of pneumothorax are most often located in the upper zones.

A recent report of four cases of subpulmonary pneumothorax (Christensen and Dietz, 1976) stressed the importance of pleural adhesions in the upper pleural space causing the pneumothorax to localize in a basal position. We wish to emphasize that subpulmonary pneumothorax can probably occur without pleural adhesions, that it may be especially common with basal penetrating trauma and that the thoracic bases and not simply the apices must be diligently searched for early small pneumothoraces.

MATERIALS AND METHODS

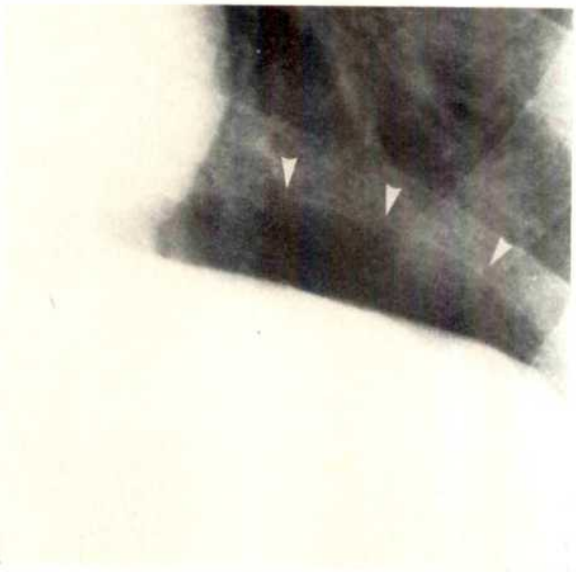
During a recent period of eight months, we have seen seven cases of pneumothorax presenting initially in an entirely subpulmonary situation. Four of them were due to penetrating stab wounds of the left lower chest, two to blunt assault on the left side of the chest without radiographic or clinical evidence of fractured ribs, and one to pulmonary metastases from a femoral osteosarcoma.

One patient had treated, healed tuberculosis in both upper lobes, but none of the others had clinical or radiographic evidence of pre-existing lung or pleural disease.

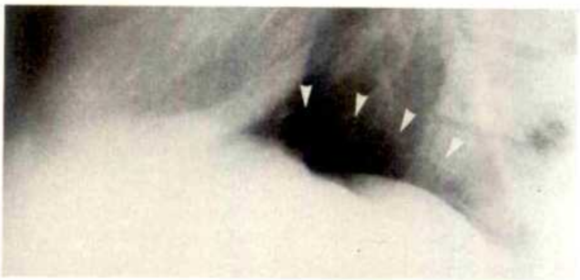
In five cases, at least some of the subpulmonary air later moved into more common sites, lateral or medial to the lung and even eventually up to the apex; this occurred after lying the patient on his side for decubitus radiographs or simply with the passage of 24 to 48 hours.

In five cases, the subpulmonary pneumothorax showed the typical appearance, *i.e.* a band of radiolucency without septa or lung markings paralleling the upper surface of the hemi-diaphragm and separated from the lung by a thin hair-line representing the basal visceral pleura (Figs. 1–3).

Two cases, due to penetrating and blunt trauma respectively, were atypical presumably due to the additional presence of blood in the pleural space. In



(A) Erect P.A. film.



(B) Erect lateral film.

FIG. 1. *Case 1.*

A 26-year old man received two stab wounds in posterior aspect of left hemithorax causing small subpulmonary pneumothorax. See line of visceral pleura (arrow-heads). Later the same day, a repeat film showed that the air had moved to the apex.

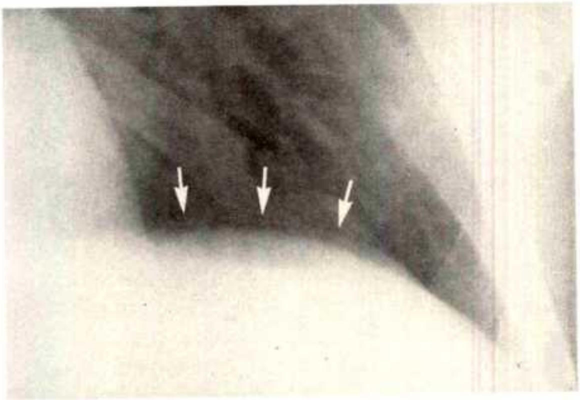


FIG. 2. *Case 2.*

Erect P.A. film. A 31-year old man stabbed in back of left hemithorax causing small subpulmonary pneumothorax. Paralleling upper surface of diaphragm is the thin line of visceral pleura (arrows).

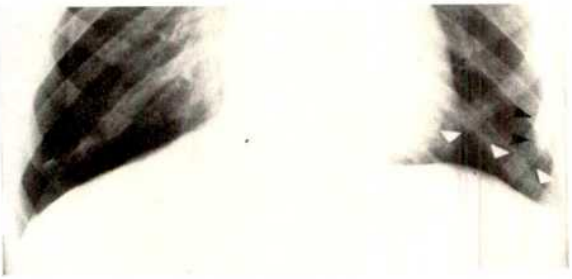
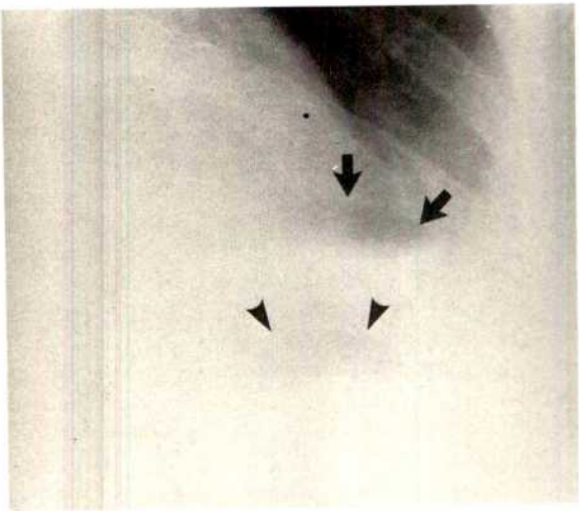


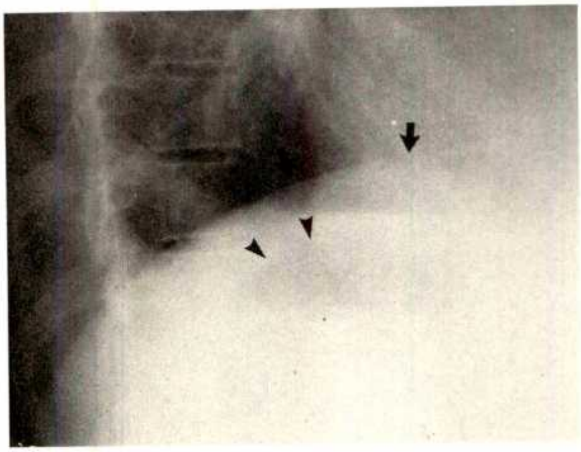
FIG. 3. *Case 3.*

Erect P.A. film. A 17-year old boy seven months after amputation for femoral osteosarcoma. The pneumothorax on the left is purely subpulmonary (white triangles), that on the right is all around the lung. Whole lung tomography confirmed that the opacity at the left base (arrow-heads) was a metastasis projecting inwards from the visceral pleura and that there were multiple metastases in both lungs; proven by thoracotomy and histology.

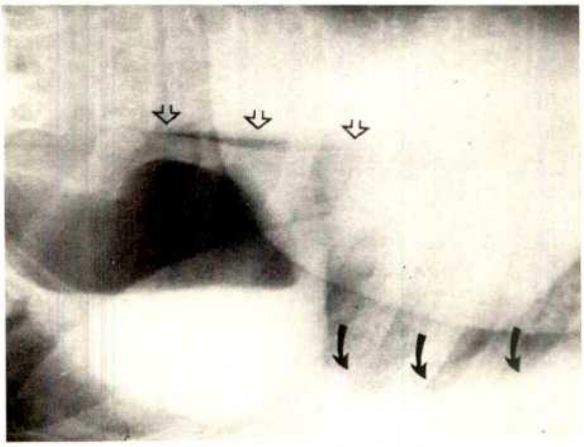
one, the blood and air formed a rounded collection with a fluid level above the stomach bubble (Figs. 4A & B). Barium examination of the stomach was entirely normal, while decubitus radiographs showed that the gas moved freely within the pleural space,



(A) Erect PA film.



(B) Erect lateral film.



(C) Left lateral decubitus film with barium in stomach.

FIG. 4. *Case 4.*

A 25-year old woman received four stab wounds in back of chest inflicted with screwdriver. In A and B, note the air-fluid collection (straight black arrows) at the left base above the stomach bubble (arrow-heads). Diagnosis—subpulmonary haemopneumothorax?, traumatic pneumatocoele?, traumatic hernia? Barium meal showed no gastric herniation. Decubitus film (C) shows the air moving freely upwards in the pleural cavity (open arrows) and the blood freely downwards (curved arrows). Diagnosis—subpulmonary haemopneumothorax.

thus excluding both traumatic herniation of the gastric fundus and traumatic pneumatocoele (Fig. 4C). In the other case (Fig. 5), the air collection at the base was crossed by numerous septa causing it to resemble bowel. Again, traumatic herniation was considered but barium examinations of stomach and colon were normal. Following drainage of the subpulmonary pneumothorax, chest radiographs were normal.

The patient with osteosarcoma metastases had been treated by amputation, radio-therapy and cytotoxic drugs. Routine chest radiographs were normal until seven months after amputation when, although the patient was asymptomatic, there were bilateral pneumothoraces and pulmonary metastases on the visceral pleura (Fig. 3). The right sided pneumothorax encircled the lung while that on the left side was purely subpulmonary.

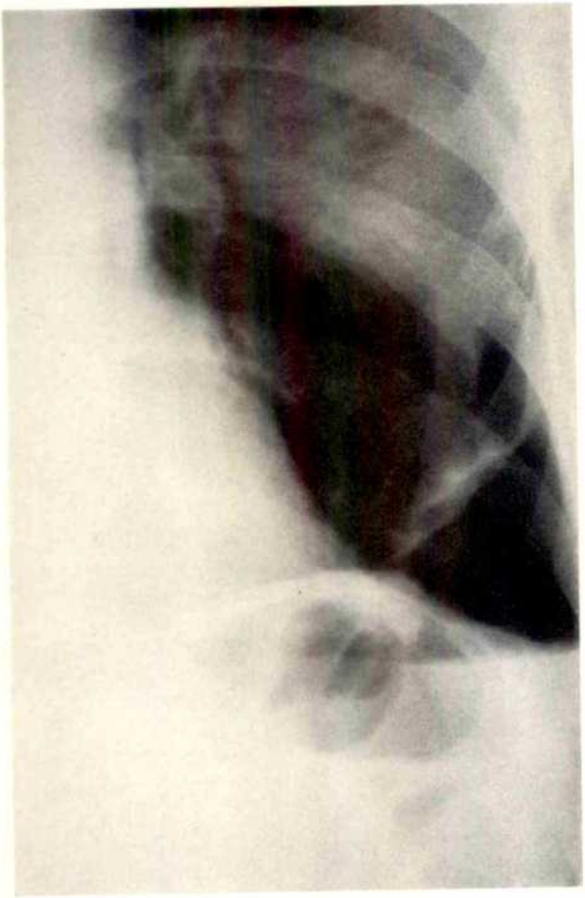


FIG. 5. *Case 5.*

Erect PA film, left basal detail. A 24-year old man was assaulted receiving blunt skull and facial injuries with amnesia. No clinical or radiographic evidence of fractured ribs but this multi-septate air collection appeared at the left base. Contrast studies of stomach, jejunum and colon were normal, excluding traumatic herniation. Following basal pleural aspiration, chest radiographs became normal. Diagnosis—subpulmonary haemopneumothorax.

DISCUSSION

Radiologists are trained to look meticulously at the apices for the earliest evidence of small pneumothorax, and recent text books (Fraser and Paré, 1970; Crofton and Douglas, 1975; Harris and Harris, 1975) make no mention of pneumothorax located in the initial stages below the lung base even in erect patients. Our series indicates that, especially in cases of penetrating trauma, one should look most carefully for the fine hair-line of visceral pleura pushed upwards from the hemi-diaphragm by a subpulmonary pneumothorax.

It is presumably the bridge-like disposition of the pleural space between the dome of the hemi-diaphragm and the hollowed out base of the lung that allows pneumothorax, arising from injury or disease of this part of the lung, to collect here. Part of the reason why this is seen so seldom is that the major causes of pneumothorax, *i.e.* pleural blebs and emphysematous bullae, are situated most commonly in the upper parts (Crofton and Douglas, 1975).

Neonatal pneumomediastinum is occasionally associated with air loculated below the lung and this is thought to be extra-pleural, between the parietal pleura and the hemi-diaphragm (Lillard and Allen, 1965; Caffey, 1972). However, none of our patients had pneumomediastinum and in five of them, some or all of the subpulmonary air later moved into more typical intrapleural sites around or above the lung after some time or after lying the patient on his side for decubitus radiographs. Indeed, it would be difficult for air to track far beneath the parietal pleura as it is found to be firmly adherent to underlying tissue during thoracic surgical dissections.

It is also unnecessary to postulate the presence of pleural adhesions higher up causing a subpulmonary situation (Christensen and Dietz, 1976) as in six of our cases there was nothing to suggest previous pulmonary or pleural disease and again because of the later movement of some of the air into higher parts of the pleural space.

The typical appearance of subpulmonary pneumothorax is a radiolucent zone without bronchovascular markings or septa lying on the hemi-diaphragm and bounded above by the thin hair-line of the visceral pleura paralleling the dome of the hemi-diaphragm (Figs. 1–3). This appearance should be diagnostic but can be confirmed by the free movement of the air into other parts of the pleural space after lying the patient on his side.

A subpulmonary pneumothorax crossed by strands of partially clotted blood producing a multiseptate appearance (Fig. 5) can resemble basal bullae or the fold or haustral pattern of bowel herniated through a diaphragmatic laceration. The latter is easily excluded by barium study of stomach and colon (Fataar and Schulman, 1978). If the blood produces a fluid level within the loculated air (Figs. 4A and B) it can again resemble traumatic herniation as well as traumatic pneumatocoele (Fagan and Swischuk, 1976; Freed, 1977) but decubitus radiographs show independent movement of the air upward and the blood downward to opposite extremities of the pleural space thus proving that the collection is intrapleural and not intrapulmonary.

The visceral pleura is much thinner than the hemi-diaphragm so that subpulmonary air should not be mistaken for subdiaphragmatic air.

We are unable to account for the fact that all seven of our cases were left sided. It can be argued that when facing a right handed assailant, the left side of the chest is more likely to receive the stab wound. However, in three of the four cases of stab wounds, they were in fact in the back of the chest.

Pulmonary metastases are a known cause of pneumothorax which for obvious reasons may be bilateral (Janetos and Ochner, 1963; Wright, 1976; Winter, 1976; Kai-Yui Yeung and Bonnet, 1977). The majority of published cases have been due to sarcomas of various origins, the commonest being osteosarcoma and most frequently in children and adolescents. Subpulmonary pneumothorax has not been reported.

Our two cases due to blunt trauma had a pneumothorax in spite of no evidence of rib fracture or penetrating injury. The presence of rib fractures is underestimated by radiological examination but even in the absence of fractures, blunt trauma can produce both lung damage and pneumothorax (Gerblich and Kleinerman, 1977).

REFERENCES

CAFFEY, J., 1972. *Pediatric x-ray diagnosis, Vol. I*, 6th edn. pp. 431–434 (Year Book Medical Publishers).

CHRISTENSEN, E. E., and DIETZ, G. W., 1976. Subpulmonic pneumothorax in patients with chronic obstructive pulmonary disease. *Radiology*, *121*, 33–37.

CROFTON, J., and DOUGLAS, A., 1975. *Respiratory diseases*, 2nd edn. pp. 350–359 and 478–487 (Blackwell Scientific Publications, Oxford).

FAGAN, C. J., and SWISCHUK, L. E., 1976. Traumatic lung and para-mediastinal pneumatocoeles. *Radiology*, *120*, 11–18.

FATAAR, S., and SCHULMAN, A., 1978. The diagnosis of diaphragmatic tears. *British Journal of Radiology* (in press).

FRASER, R. G., and PARE, J. A. P., 1970. *Diagnosis of diseases of the chest*, Vol. 1, pp. 371–376 (W. B. Saunders Company, Philadelphia).

FREED, C., 1977. Traumatic lung cysts after penetrating chest injury (report of three cases). *South African Medical Journal*, *51*, 720–722.

GERBLICH, A. A., and KLEINERMAN, J., 1977. Blunt chest trauma and the lung (editorial). *American Review of Respiratory Diseases*, *115*, 369–371.

HARRIS, J. H., and HARRIS, W. H., 1975. *The radiology of emergency medicine*. pp. 226–230. (Williams and Wilkins, Baltimore).

JANETOS, G. P., and OCHNER, S. F., 1963. Bilateral pneumothorax in metastatic osteogenic sarcoma. *American Review of Respiratory Diseases*, *88*, 73–76.

KAI-YUI YEUNG and BONNET, J. D., 1977. Spontaneous pneumothorax with metastatic malignant melanoma. *Chest*, *71*, 435–436.

LILLARD, R. L., and ALLEN, R. P., 1965. The extrapleural air sign in pneumomediastinum. *Radiology*, *85*, 1093–1098.

WINTER, W. G., 1976. Spontaneous pneumothorax heralding metastasis of adamantinoma of tibia. *The Journal of Bone and Joint Surgery (American Volume)*, *52*, 416–417.

WRIGHT, F. W., 1976. Spontaneous pneumothorax and pulmonary malignant disease—a syndrome sometimes associated with cavitating tumours. *Clinical Radiology*, *27*, 211–222.

Book review

Computerised cranial tomography. Edited by B. Felson, pp. 146, illus., 1977 (New York; Grune and Stratton Inc.) $18.50/£13·15.

This book presents a collection of papers which were originally published in seminar in *Radiolgoy* Vol. 12. Each of the major papers is a good, well illustrated review of its subject. The presentation on equipment and physics by Tor-Pogossian stands out as a model of clarity in explaining this difficult field to diagnostic radiologists.

This book is not meant to be comprehensive and there are obvious omissions as for example, the lack of consideration of hydrocephalus or the effects of surgery and other therapy. The defects are covered to some extent in the good selection of references.

It is recommended as an authorative introduction to cranial computed tomography.

B. E. KENDALL.

1978, *British Journal of Radiology*, *51*, 498–502

Lateral lumbar discography

By J. A. McCulloch, M.D., F.R.C.S. (C), and G. Waddell, B.Sc., M.D.(Glas.), F.R.C.S.(Edin.)*

Department of Orthopaedic Surgery, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8

(*Received November, 1977 and in revised form February, 1978*)

ABSTRACT

The technique of lateral lumbar discography is described and compared with that of posterior lumbar discography. Its safety is demonstrated in a series of 1500 patients, only four of whom developed complications of note. Of these four, three developed discitis and one a retroperitoneal haemorrhage, all of which settled with conservative treatment.

Since its introduction by Lindblom (1948), lumbar discography has been widely used for the investigation of lumbar disc disease, although the initial enthusiasm has waned in Scandinavia (Hirsch, 1965) and is under question in North America (Holt, 1968; Rothman and Simeone, 1976; Epstein, 1976). The interpretation and limitations of discography will not be discussed here (Fernstrom, 1960; Collis and Gardner, 1962; Feinberg, 1964; Holt, 1968; Gresham and Miller, 1969; DePalma and Rothman, 1970; Finneson, 1973; Rothman and Simeone, 1976; Epstein, 1976), except to emphasize that discography is but one supplementary technique in the investigation of lumbar disc disease and the results must be correlated with other radiological and clinical information. The radiological pattern, the resistance to injection, and the patient's subjective response must all be considered. At present, lumbar discography is mainly used to demonstrate a normal disc space above a proposed fusion level, in the investigation of a possible pseudarthrosis and as a prelude to chemonucleolysis or the injection of chymopapain.

Most reports have described mid-line, transdural discography, although Erlacher (1952) and Keck (1960) suggested a postero-lateral approach (Fig. 1). The risks of intradural injection of chymopapain (Smith and Brown, 1967; Shealy, 1967) have since stimulated the development of a lateral, extradural approach (Smith and Brown, 1967; Day, 1969; Brown, 1969; Finneson, 1973). This communication describes the technique, advantages and safety of lateral lumbar discography.

TECHNIQUE

Lateral discography may be carried out in the operating room or X-ray department under aseptic conditions and local anaesthesia. Pre-operative sedation may be given. The patient is placed on his left side on a radiolucent table. A portable image intensifier is used to provide both lateral and A.P. views of the spine (Fig. 2). A folded sheet is placed beneath the left flank to provide sufficient support and to correct any scoliosis. The patient reduces the lumbar lordosis by flexing the neck, hips and knees. The image intensifier is positioned so that the discs are adequately demonstrated and a true lateral view is obtained in both the coronal and transverse planes.

The skin is prepared and draped in a routine manner. A standard discography tray contains 1% Xylocaine, three 10 ml syringes, disposable needles for local anaesthetic infiltration, a metal cup for contrast medium and non-disposable needles foı introducing contrast, in the following sizes: a 4 in. no. 18, a 6 in. No. 18 and a 6 in No. 22. Non-disposable needles are preferred because of the sensation that is obtained when the blunt tip encounters the annulus of a disc. This "feeling" is not obtained from sharp disposable needles.

L. 4–5 disc space

The L. 4–5 disc space is approached first from a point at the level of the iliac crest and 10 cm (one hand's breadth) to the right of the mid-line. The distance from the mid-line may be varied slightly to allow for the patient's build. If muscle spasm interferes with localization of the spinous processes, the mid-line may be identified first in the lower thoracic region.

After superficial infiltration of local anaesthetic, the 6 in. No. 18 needle is inserted at an angle of 50–60 deg. to the sagittal plane in the direction of the L. 4–5 disc space. The lateral radiograph confirms that the needle is neither superior nor inferior to the disc space. If necessary, further local anaesthetic may be infiltrated through the needle. Two important technical considerations are mentioned below.

When the tip of the advancing needle reaches a line adjoining the posterior borders of the vertebral bodies, the examiner should obtain a firm, gritty sensation from the annulus (Figs. 3 and 4A). If the tip of the needle passes anterior to this line before this sensation is obtained (Fig. 4B), the needle will not bisect the disc, but will pass antero-lateral to it. If this occurs, the angle of needle insertion is too

---

*Present Address: Department of Orthopaedic Surgery, Western Infirmary, Glasgow, G11 6NT.

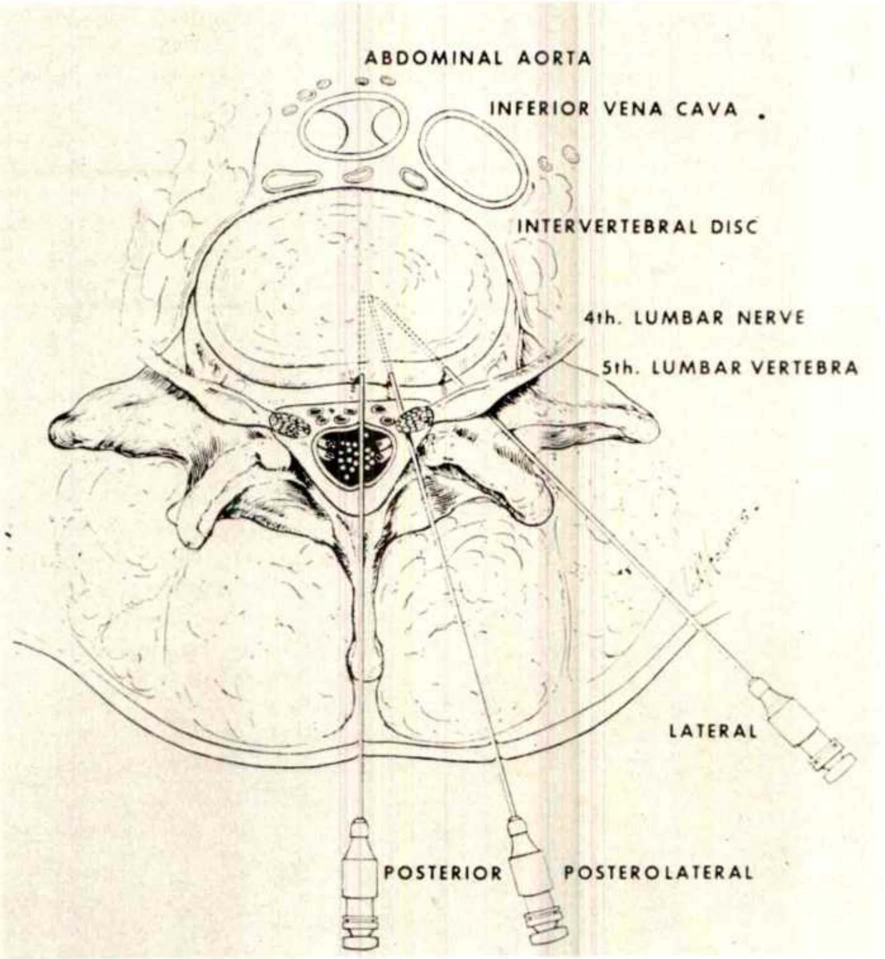


FIG. 1.
The various approaches for discography. Reproduced with permission from Smith and Brown, 1967 and the publishers.

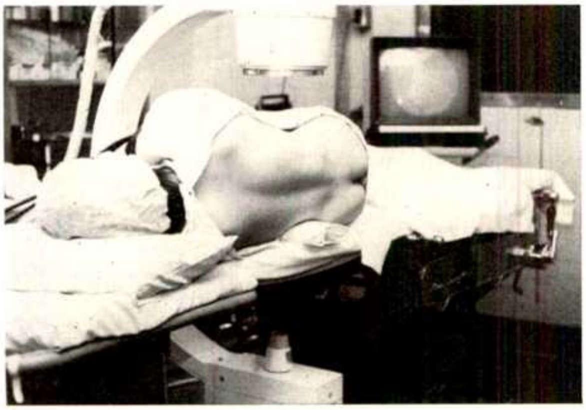


FIG. 2.
Patient positioned for lateral discography.

close to 45 deg. and should be changed nearer to 60 deg. to the sagittal plane. When changing the angle, the needle should first be withdrawn close to the skin surface.

The second important consideration relates to bony obstruction from the transverse process, the pars interarticularis or the facet joint. Which of these structures causes obstruction can be determined on the lateral radiograph (Fig. 5). Bony impingement at the level of the upper half of the vertebral body is probably due to the transverse process. Obstruction at the level of the lower half of the vertebral body is probably due to the pars interarticularis. Opposite the disc space, obstruction is probably due to the facet joint. If the transverse process causes obstruction, the site of needle insertion is moved in a

Results

Latent Period

The relationship between the dose of 250 kV X rays to the spinal cord and the latent period for development of partial paralysis is shown in Fig. 1 which gives the results after single doses and after two, four, eight, 15 or 30 equal fractions of radiation.

It can be seen that paralysis following irradiation of the lumbar cord appears after a minimum period of between 100 and 140 days. Following doses of radiation which are large enough to give rise to a high probability of paralysis, the latent period appears to be independent of the dose given. It is also independent of the fractionation schedule employed, being of similar duration following a single dose, two equal doses separated by different intervals of time, and four or eight equal doses in six weeks.

At the lower doses used for each fractionation schedule the mean latent period for those animals showing paralysis was longer, indicating that at doses causing a low incidence of paralysis the latent period was inversely related to dose. After the highest doses given in 15 and 30 fractions less than 100% of rats had become paralysed even at one year after irradiation. The latent period was, therefore, much longer; no rats succumbed to spinal cord damage within 200 days after irradiation with 15 or 30 fractions.

TABLE I

ED_{50} following two equal doses of X rays separated by varying times

Treatment	ED_{50} (rad) $\pm 2\times$ variance
Single dose	2400 ± 80
2F/1d 1st expt.	3350 ± 100
2nd expt.	3300 ± 100
2F/4d	3200 ± 240
2F/8d	3250 ± 200
2F/16d	3250 ± 200
2F/32d	3650 ± 200

Overall treatment time (*T*)

The proportion of animals showing ataxia and loss of the extension reflex of the hind limbs at six months after treatment was plotted against total dose for animals given two equal doses of X rays separated by periods of time ranging from one day to 32 days (Fig. 2). The effect of single doses of X rays is shown for comparison. The doses of X rays which produced paralysis of the hind legs in 50% of the rats (ED_{50}) were derived from these curves and are given in

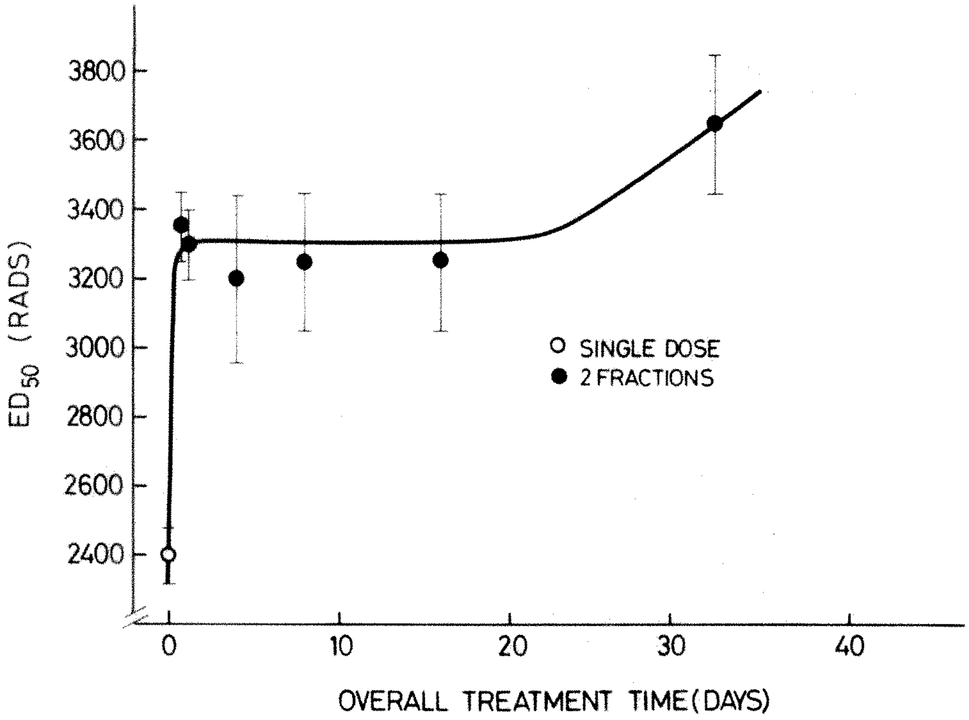


Fig. 3.

Relationship between ED_{50} and overall treatment time. Bars show variance.

1978, *British Journal of Radiology*, *51*, 515–523 JULY 1978

Radiation damage to the rat spinal cord: the effect of single and fractionated doses of X rays

By Ann White, PhD., B.Sc., and Shirley Hornsey, D.Sc.

MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W12 OHS

(*Received September, 1977 and in revised form January, 1978*)

ABSTRACT

The tolerance of the rat lumbar spinal cord to single and multiple doses of X irradiation has been studied using paralysis of the hind legs as the endpoint. The paralysis, which has an acute onset progressing from the first symptoms to full paralysis within two to three days, occurs within one year post-irradiation. Dose/effect relationships were estimated at one year. Experiments which were designed to study the effect of varying the overall treatment time between two equal doses of X rays showed that a large amount of recovery from irradiation damage occurred during the first 24 hours after irradiation (D_2–D_1 at 24 hours was 950 rad). No further recovery took place for another 15 days but at 32 days another wave of recovery seemed to be in progress (D_2–D_1 at 32 days was 1250 rad).

The effect of varying the number of fractions independently of the overall treatment time was investigated. The tolerance of the cord increased rapidly as the number of fractions given in a six-week period was increased from four to 30. The slope of a Strandqvist-type plot of this data was about 0.4. The data for the spinal cord have been compared with similar data for late damage in the mouse lung.

The latent period between irradiation and the onset of paralysis was also investigated. At high doses, when the probability of paralysis occurring was great, the latent period was independent of the dose. At lower doses which gave rise to a lower incidence of paralysis, the latent period was inversely related to the dose.

A second type of paralysis occurred later than one year after irradiation. This had a very protracted development and occurred in unirradiated as well as irradiated animals.

The spinal cord is sometimes unavoidably included in the treatment fields used in radiotherapy. This can result in the development of myelopathy after periods ranging from a few months to several years. The response of normal nervous tissue is thus an important factor limiting the dose of irradiation to which some tumours can be exposed. It is therefore desirable to determine the tolerance of the spinal cord to irradiation and particularly to determine the relationships between limiting dose and fractionation.

The dose of irradiation which normal tissues can tolerate varies with the number of fractions (N) in which the dose is given and with the overall treatment time (T). Ellis (1969) has proposed that the relationship between the dose which a tissue will tolerate, the number of fractions and the overall treatment time is described by the formula

$$\text{tolerance dose} \propto N^{\alpha}\, T^{\beta}$$

From clinical data and from experiments on pig skin (Fowler, 1965), Ellis calculated the exponents of N and T to be 0.24 and 0.11 respectively for irradiation with X rays. For lung damage using death from radiation pneumonitosis as the endpoint, Field *et al.* (1976) have calculated the exponent of T to be 0.07 while that of N appears to vary with the number of fractions given, being 0.39 for one to eight fractions and 0.25 for eight to 30 fractions.

Early studies of the effects of irradiation on the spinal cord involved the use of single, large doses of irradiation (Innes and Carsten, 1961; Carsten and Zeman, 1966; Geraci *et al.*, 1974). Recent experiments by van der Kogel (1977a and b) have shown that the tissue tolerance curve for late damage to the spinal cord from one to twenty fractions has a slope of about 0.44. In his experiments the tissue tolerance was unaffected by variations in the overall treatment time unless this was extended to periods greater than eight weeks.

The experiments described in this paper were designed to investigate the effects of varying the number of fractions of X rays and the overall time in which they are given on the development of damage to the lumbar cord of rats. Also included are some preliminary data on the cervical cord.

Van der Kogel (1977b) has suggested that there are two distinct time periods over which myelopathy develops in the rat cord. The first phase occurs after latent periods of four to seven months after irradiation: the second phase occurs after latent periods of more than one year. We have limited our observations on the dose-effect relationship to the first acute phase but have included some data on the second phase.

In general our results on the first phase confirm and extend the findings of van der Kogel but they do differ in a few specific points.

METHODS

The spinal cords of three-month-old male CFHB rats (Anglia Laboratory Animals) were irradiated in the lumbar region or in the cervical region with X rays generated by a Marconi 250 kV X-ray set, at a dose rate of 200 rad/min. The filtration used was 0.3 mm Cu and 1 mm Al giving a half-value layer of 1.35 mm Cu. To avoid damaging the gut or the

P25838

posterior, or thinnest and weakest, part of the annulus (Day, 1969) has on one occasion precipitated a cauda equina syndrome (Collis and Gardner, 1962). With the lateral approach, if a disc herniation did occur, it would be of little clinical significance.

The main disadvantage of the lateral approach is that it depends on clear, three-dimensional visualization of the anatomy. Exact positioning of the patient is vital. Posterior discography becomes anatomically more difficult on ascending the lumbar spine, while lateral discography becomes easier. Posterior discography is impossible in the presence of a posterior fusion, while lateral discography is impossible at the level of an intertransverse fusion or a complete sacralization.

The final advantage of the lateral approach is that it is easier for the patient. Fewer pain-sensitive structures are penetrated. Nerve-root encounters are less frequent. Technically, it is simple.

REFERENCES

BROWN, J. E., 1969. Clinical studies on chemonucleolysis. *Clinical Orthopaedics and Related Research*, *67*, 94–99.

COLLIS, J. S., and GARDNER, W. J., 1962. Lumbar discography; an analysis of one thousand cases. *Journal of Neuro-surgery*, *19*, 452–461.

DAY, P. L., 1969. Lateral approach for lumbar diskogram and chemonucleolysis. *Clinical Orthopaedics and Related Research*, *67*, 90–93.

DEPALMA, A., and ROTHMAN, R., 1970. In *The Intervertebral Disc*, p.247 (W. B. Saunders Company, Philadelphia).

EPSTEIN, B. S., 1976. In *The Spine: a Radiological Text and Atlas*, 4th edn, pp.148–153 (Lea and Febiger, Philadelphia).

ERLACHER, P. R., 1952. Nucleography. *Journal of Bone and Joint Surgery (Br.)*, *34B*, 204–210.

FEINBERG, S. B., 1964. The place of diskography in radiology as based on 2,320 cases. *American Journal of Roentgenology*, *92*, 1275–1281.

FERNSTROM, U., 1960. A discographical study of ruptured lumbar intervertebral discs. *Acta Chirurgica Scandinavica Supplement*, 258.

FINNESON, B. E., 1973. In *Low Back Pain*, pp.69–76 (Lippincott Company, Philadelphia and Toronto).

GARDNER, W. J. WISE, R. E., HUGHES, C. R., O'CONNELL, F. B., and WEIFORD, E. C., 1952. X-ray visualization of the intervertebral disk. *Archives of Surgery*, *64*, 355–364.

GRESHAM, J. L., and MILLER, R., 1969. Evaluation of the lumbar spine by diskography and its use in selection of proper treatment of the herniated disc syndrome. *Clinical Orthopaedics and Related Research*, *67*, 29–41.

HIRSCH, C., 1965. Efficiency of surgery in low-back disorders. *Journal of Bone and Joint Surgery* (*Am.*), *47A*, 991–1004.

HOLT, E. P., 1968. The question of lumbar discography. *Journal of Bone and Joint Surgery* (*Am.*), *50A*, 720–726.

KECK, C., 1960. Discography, technique and interpretation. *Archives of Surgery*, *80*, 580–585.

LINDBLOM, K., 1948. Diagnostic puncture of intervertebral disks in sciatica. *Acta Orthopaedica Scandinavica*, *17*, 231–239.

MASSIE, W. K., and STEVENS, D. B., 1967. A critical evaluation of discography. *Journal of Bone and Joint Surgery* (*Am.*), *49A*, 1243–1244.

ROTHMAN, R. H., and SIMEONE, F. A., 1976. In *The Spine*, p.468 (W. B. Saunders Company, Philadelphia, London, Toronto).

SHEALY, C. N., 1967. Tissue reactions to chymopapain in cats. *Journal of Neurosurgery*, *26*, 327–330.

SMITH, L., and BROWN, J. E., 1967. Treatment of lumbar intervertebral disc lesions by direct injection of chymopapain. *Journal of Bone and Joint Surgery* (*Brit.*), *49B*, 502–519.

WISE, R. E., GARDNER, W. J., and HOSIER, R. B., 1957. X-ray visualization of the intervertebral disk. *The New England Journal of Medicine*, *257*, 6–10.

Book review

Progress in pediatric Radiology. Skull, Spine and Contents. Part II Clinical Aspects. Edited by H. J. Kaufmann. pp. viii+300, illus., 1978 (Switzerland; S. Kerger AG) $49.75/DM.161.

This book contains a series of authoritative and well illustrated papers dealing with cranio-synostosis, asymmetry of the skull, the meninges, intracranial and intraspinal tumours and with shunts and their complications. The articles are comprehensive except that they do not in general consider computed tomography which in most institutions is now the primary investigation in most intracranial disorders. Despite the fact that some of the investigations are now rarely necessary, anybody interested in radiology of the nervous system will find these reviews most interesting and worthwhile reading.

There is one chapter dealing with CT demonstration of pathologic changes of the spinal cord accompanying spina bifida and diastematomyelia. In addition to reviewing the literature the paper presents the findings on 14 patients examined with plain computed tomography and clearly demonstrates the advantages of the procedure.

B. E. KENDALL.

1978, *British Journal of Radiology*, *51*, 503–506

JULY 1978

The effect of radiology electives on career choice at McMaster University

By M. S. F. McLachlan, M.D., F.R.C.P.E., F.R.C.R., and M. Herzig, M.Sc.

Department of Radiology and Programme for Educational Development, Faculty of Health Sciences, McMaster University, 1200 Main Street West, Hamilton, Ontario, Canada L8S 4J9

(*Received November, 1977*)

ABSTRACT

Recruitment to radiology is said to be affected by the extent to which radiologists participate in medical student teaching. At McMaster University, where radiologists make major contributions to the medical school curriculum, students appear to show little interest in radiology as a career. The characteristics, attitudes and career choices of students at McMaster who undertook elective periods in radiology between 1973 and 1976 were examined. Though students rated the elective experience very highly, none intended to become a radiologist. Half of the group wished to take up family practice, the proportion in the school as a whole being similar. This is consistent with policies of student selection and education at McMaster. Most of those choosing family practice did not change their career choice between entry to and exit from the school. Involvement of radiologists in the curriculum had no detectable positive influence on career choice.

Of the factors influencing recruitment of trainees in radiology, the extent of involvement of radiologists in medical student teaching has been assumed to be among the most important (Abrams, 1966; Windeyer, 1969; Bull, 1974). At McMaster University, radiologists contribute extensively to medical student teaching. The department of radiology was one of the first to be established when the medical school began ten years ago. Radiologists act as tutors, participate in rounds and make major contributions to administrative aspects of the curriculum. Large numbers of medical students spend elective periods in the departments of radiology which go to make up the school. Elective periods in many fields of interest form a large part of the McMaster curriculum and are stated by graduates to be very important in influencing their choice of career (W. B. Roy, personal communication). By 1976 nearly 300 students had graduated from the school; only one has so far chosen to become a radiologist.

This paper examines characteristics, attitudes and career choices of McMaster students who undertook electives in radiology.

THE MCMASTER CURRICULUM

Students enter the medical school after three years of undergraduate work. The curriculum and its objectives have been described in detail (Neufeld and Barrows, 1974; Hamilton, 1976). Radiology is integrated throughout the curriculum, which lasts 32 months and is divided into four phases. Phase I lasts ten weeks. It introduces students to principles of pathological mechanisms and begins to examine body function and structure, aspects of which are demonstrated by radiological methods. Phase II, which lasts 12 weeks, deals with cell biology and general principles of injury, for example inflammatory responses. It ends with an elective period of four weeks. Phase III consists of four units, each of ten weeks. These deal with major body systems, normal and abnormal being considered together. There is no formal course in anatomy; radiology is used to teach anatomy and pathology. One of the units, concerned with haematology and gastroenterology, is described by Ali *et al.*, 1977. Radiologists frequently act as tutors in Phase III; for ten weeks they spend at least four hours each week with a group of four or five students. Another elective period, of six weeks, occurs during this phase. Phase IV lasts nearly one year. Students spend between four and eight weeks in each of the major disciplines, for example, medicine or obstetrics and gynaecology, and are responsible, under supervision, for care of patients. Most elective periods are undertaken during or immediately before this phase, 16 weeks being set aside for the purpose.

Electives in radiology are usually undertaken in one of the five teaching hospitals of which the school is composed. Collectively these hospitals contain well over 2000 active beds and are staffed by 25 radiologists, of whom seven hold full-time university appointments and 12 hold part-time appointments. During elective periods students participate in the work of the department, as individuals or in groups of two to four. They observe procedures, join conferences and reporting sessions and participate in tutorials. Excellent libraries of radiographs, books and audio-visual materials are readily available.

METHODS

Before students started the elective period in radiology they were asked to state, in order of importance, the reasons for their choice. The dates

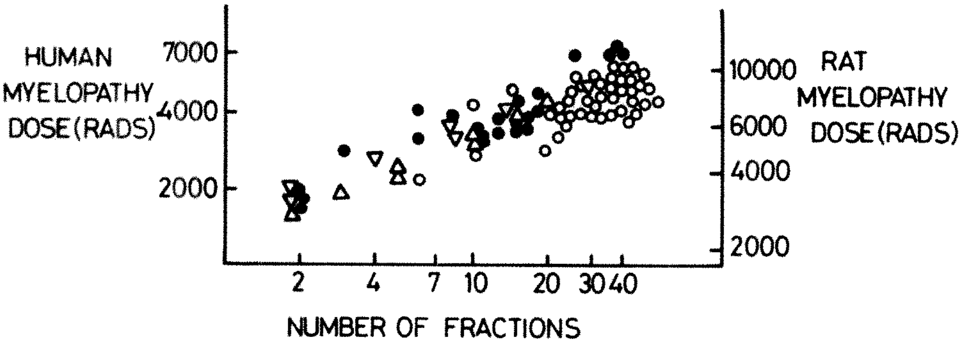


FIG. 7.

The incidence of myelopathy in patients receiving irradiation (1–4 MV X rays or Co^{60} γ rays) to the thoracic cord (Wara *et al.*, 1975) compared with the incidence in rats given doses to the cervical or lumbar cord (250 kV X rays).
● patients with myelopathy. ○ patients without myelopathy.
△ myelopathy in 50% of rats, Van der Kogel 1977,
▽ myelopathy in 50% of rats, present data.

Field *et al.* (1976) found that in lung the first rapid, phase of recovery following irradiation was followed by a much slower phase which continued up to 60 days after irradiation. The exponent of the T factor was found to be 0.07. To account for this they have suggested a process of slow repair of radiation damage similar to Elkind repair of sublethal damage but taking about 100 times as long. They have postulated that this slow repair process may be typical of slowly proliferating tissues such as kidney and liver. However, on the basis of the results presented here and also those of van der Kogel (1976), this type of slow repair does not occur in the rat spinal cord and such sparing as occurs with long overall treatment times could be explained by a wave of repopulation stimulated during the treatment period.

The effect of increasing the treatment time on the dose required to cause damage to the cord is so small as to have little bearing on the planning of radiotherapy schedules. Considerable sparing of the spinal cord is, however, likely to be achieved by using large numbers of fractions. It is interesting that although the type of damage caused by irradiation of the two regions of cord is different, the effects of dose fractionation are very similar. In both the lumbar and cervical cords the ED_{50} increases from 2400 rad for a single dose to just over 6000 rad for eight fractions in six weeks. This may indicate that the relationship between tolerance dose and fractionation established here for damage to the lumbar and cervical cord may be applied to all regions of the spinal cord. A correlation between the isoeffect relationship of radiation myelopathy in the rat spinal cord and that observed in patients is shown in Fig. 7. The data on patients are these published by Wara *et al.* (1975) on the thoracic cord and are compared with data on the cervical and lumbar cord of rats presented here. The rat data have been normalized to the human value at two fractions; the absolute doses for rat myelopathy would be about 1.8 times higher than the doses producing myelopathy in humans. A line drawn through the data from patients who received from two to 40 fractions and developed myelopathy has a similar slope to that for the animal data, *i.e.* 0.40. This shows that the animal data gives a good model for the human response and gives confidence in extrapolating from animal data to areas outside clinical experience. It also confirms the view, drawn from the measured response to fractionated treatment of the animal cord, that the best sparing of damage to the spinal cord can be obtained by extended fractionation of dose.

REFERENCES

CARSTEN, A., and ZEMAN, W., 1966. The control of variables in radio-pathological studies in mammalian nervous tissue. *International Journal of Radiation Biology, 10,* 65–74.

CAVANAGH, J. B., 1968. Effects of X-irradiation in the proliferation of cells in peripheral nerve during Wallerian degeneration in the rat. *British Journal of Radiology, 41,* 275–281.

ELLIS, F., 1969. Dose, time and fractionation: a clinical hypothesis. *Clinical Radiology, 20,* 1–8.

FIELD, S. B., HORNSEY, SHIRLEY, and KUTSUTANI, Y., 1976. Effects of fractionated irradiation on mouse lung and a phenomenon of slow repair. *British Journal of Radiology, 49,* 700–707.

FOWLER, J. F., 1965. The estimation of total dose for different numbers of fractions in radiotherapy. *British Journal of Radiology, 38,* 365–368.

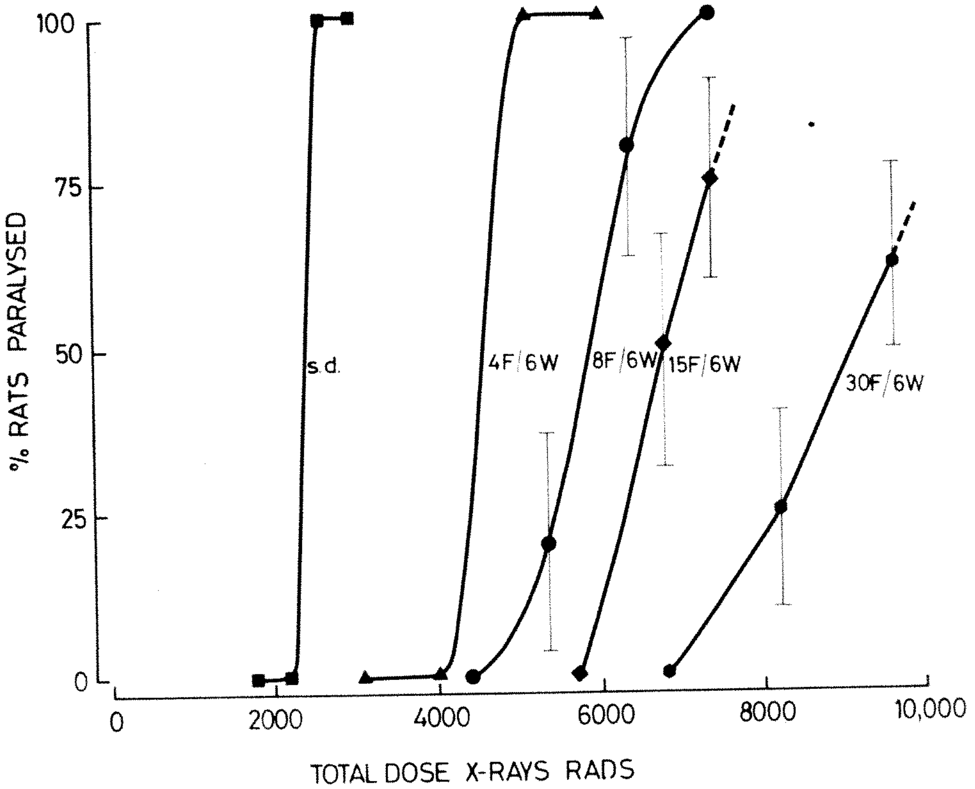


Fig. 4.

Dose-effect curves for a single dose and for four, eight, 15 and 30 equal doses of X rays to the lumbar cord in six weeks.

TABLE II

ED$_{50}$ following four, 8, 15 or 30 equal doses of X rays in six weeks

Treatment	Region	ED$_{50}$ (6 months) (rad) $\pm 2 \times$ variance	ED$_{50}$ (1 year) (rad) $\pm 2 \times$ variance
Single dose	Lumbar	2400 ± 200	2400 ± 200
4F/6W	Lumbar	5000 ± 400	4600 ± 500
8F/6W	Lumbar	6200 ± 400	5900 ± 250
15F/6W	Lumbar	—	6800 ± 400
30F/6W	Lumbar	—	9200 ± 600
Single doses	Cervical	2400 ± 200	—
8F/6W	Cervical	6300 ± 400	—

Table I. ED$_{50}$ values obtained for treatments involving two doses of X rays using either the date of the first dose or the mid-point of the fractionated series were identical. Unfortunately, these animals contracted a lung infection and had to be killed at about nine months after irradiation and so no data are available on them at later times. However, very few rats had succumbed to spinal cord damage between six and nine months after irradiation.

The ED$_{50}$ values from Table I are plotted against overall treatment time in Fig. 3. This shows that considerable recovery from radiation damage occurs during the first 24 hours after irradiation. (D_2–D_1) at 24 hours is 950 rad. There seems to be no additional recovery from the damage inflicted by the first dose of irradiation during the next 15 days. However, at 32 days a second wave of recovery seems to be under way for (D_2–D_1) increases to 1250 rad between 16 and 32 days. Increasing the overall treatment time from one to 16 days, therefore, gives little sparing of the lumbar cord. With treatment times longer than 16 days the total dose of irradiation which the cord will tolerate increases. Preliminary observations on the cervical cord appear to support these results and will be reported elsewhere.

Number of fractions N

The ED$_{50}$ values at six months and one year after irradiation were derived graphically in the same way as for the two fraction experiment. The dose-effect curves for the lumbar cord at one year after irradiation are shown in Fig. 4 and the ED$_{50}$ values to demands for more family doctors, manpower shortages are predicted in North America also (Potchen, 1976; Riemenschneider, 1977). Greater involvement of radiologists in medical student teaching may not, by itself, influence that trend.

Acknowledgments

Mrs. Jane Hamilton, Drs. Barbara Ferrier, R. McAuley, V. Neufeld, D. Rosenthal and W. Walsh and Mr. F. Bradley provided much useful comment and information. We are especially grateful to Ms. Wendy Roy and Dr. Chris Woodward of the Programme for Educational Development at this school for details of career choices of McMaster students and how these are influenced.

REFERENCES

Abrams, H. L., 1966. Diagnostic radiology in the medical school: quandary or crisis? *Journal of Medical Education, 41*, 850–859.

Ali, M. A. M., Thomas, E. J., Hamilton, J. D., and Brain, M. C., 1977. "Blood and guts": one component of an integrated program in biologic sciences as applied to medicine. *Canadian Medical Association Journal, 116*, 59–62.

Bull, J. W. D., 1974. What is diagnostic radiology's place in medicine? *British Medical Journal, 3*, 394–400.

Deschênes, S. M., 1977. Etudiants inscrits aux facultés de médecine du Canada, 1976–77. *Canadian Medical Association Journal, 117*, 783–786.

Donovan, J. C., Salzman, L. F., and Allen, P. Z., 1972. Studies in medical education: career choice consistency of medical students. *American Journal of Obstetrics & Gynecology, 112*, 519–523.

Dubé, W. F., and Johnson, D. G., 1976. Study of U.S. medical school applicants, 1974–75. *Journal of Medical Education, 51*, 877–896.

Gough, H. G., 1975. Specialty preferences of physicians and medical students. *Journal of Medical Education, 50*, 581–588.

Hamilton, J. D., 1976. The McMaster curriculum: a critique. *British Medical Journal, 1*, 1191–1196.

Held, M. L., and Zimet, C. N., 1975. A longitudinal study of medical specialty choice and certainty level. *Journal of Medical Education, 50*, 1044–1051.

Keettel, W. C., 1972. Discussion of studies in medical education: career choice consistency of medical students by Donovan *et al. American Journal of Obstetrics & Gynecology, 112*, 523–525.

Lamarche, G., and Deschênes, M., 1976. Medical school applicants in Canada. *Association of Canadian Medical Colleges Forum, 9*, 6–20.

Last, J. M., and Stanley, G. R., 1968. Career preference of young British doctors. *British Journal of Medical Education, 2*, 137–155.

Monk, M. A., and Thomas, C. B., 1970. Characteristics of male medical students related to their subsequent careers. *Johns Hopkins Medical Journal, 127*, 254–272.

Neufeld, V. R., and Barrows, H. S., 1974. The "McMaster philosophy": an approach to medical education. *Journal of Medical Education, 49*, 1040–1050.

Oates, R. P., and Feldman, H. A., 1974. Patterns of change in medical student career choices. *Journal of Medical Education, 49*, 562–569.

Parkhouse, J., and McLaughlin, C., 1976. Career preferences of doctors graduating in 1974. *British Medical Journal, 2*, 630–632.

Parkhouse, J., and Palmer, M. K., 1977. Career preferences of doctors qualifying in 1975. *British Medical Journal, 2*, 25–27.

Phelps, C. E., 1968. Women in American medicine. *Journal of Medical Education, 43*, 916–924.

Potchen, E. J., 1976. Diagnostic radiology—planning for the future. *Radiology, 120*, 227–229.

Riemenschneider, P. A., 1977. Radiology manpower update, 1976: shortage or surfeit. *American Journal of Roentgenology, 129*, 575–582.

Shapiro, C. S., Stibler, B. J., Zelkovic, A. A., and Mausner, J. S., 1968. Careers of women physicians: a survey of women graduates from seven medical schools, 1945–1951. *Journal of Medical Education, 43*, 1033–1040.

Westling-Wikstrand, H., Monk, M. A., and Thomas, C. B., 1970. Some characteristics related to the career status of women physicians. *Johns Hopkins Medical Journal, 127*, 273–286.

Windeyer, B., 1969. Education in radiology. *Clinical Radiology, 20*, 241–246.

Book review

Radiology and Injury in Sport. By J. W. Bowerman, pp. xix + 330, illus., 1977 (New York; Appleton-Century-Crofts) £21·20.

This is a 320 page review book of the injuries sustained during sporting activities. It is basically divided into two halves, the first of which deals with the radiographic assessment of injuries at various anatomical sites. The second half is a review of the incidence and type of injury related to different sporting activities.

The text outlines all the commoner injuries with explanation and theories about the mechanisms involved. Timely reminders of the nature of individual sports are given with this in mind *e.g.* under cricket "Those not familiar with cricket should be reminded that the bowler runs toward the batsman before releasing the ball". Each chapter is supported by a considerable number of references.

There are abundant radiographs throughout the book of varying quality and these are supported by line drawings. One very irritating feature, to me, is the use of pencil/pen enhancement of fracture lines on the radiographs. With supporting line drawings to help, this sort of artistic interference should not be necessary.

Some of the statistics quoted are rather staggering and certainly the book has a real appeal to those involved or interested in trauma or sport. One other feature of note was the world review of rugby in England, New Zealand, Ireland and South Africa without mention of W – – – s!

This book is a useful addition to casualty and accident and emergency departments as well as the radiological library.

A. B. Ayers.

1978, *British Journal of Radiology*, *51*, 507–514

Dosimetry of cathetron applicators in intracavitary therapy

By A. V. Santhamma, M.Sc., and K. R. Das, M.Sc.

Division of Radiological Protection, Bhabha Atomic Research Centre, Trombay, Bombay 400 085, India

(*Received July, 1977 and in revised form December, 1977*)

ABSTRACT

Theoretical computations have been done to obtain dose distributions in the paracervical and sagittal planes for various loadings of Cathetron applicators. Uterine catheters of various sizes and shapes and various loadings of ovoid catheters have been considered for the dosimetry. Experimental measurements have been made to verify the computed dose distributions. The computed dose distributions have also been compared with those of a conventional Manchester loading. Although the ratio of dose contribution to point A from vaginal sources to that from the uterine sources is found to be significantly different for Cathetron therapy from the conventional Manchester system, the isodose distributions in the paracervical plane are in good agreement. However, the difference in the isodose distributions in the sagittal plane indicates a higher dose to the rectal region for Cathetron therapy, which can be reduced by the use of rectal retractors.

High-intensity, remote-controlled after-loading devices make possible the elimination of practically all the radiation exposure to staff during intracavitary applications. Of the number of such units currently in use in various radiotherapy centres throughout the world, the Cathetron (O'Connell *et al.*, 1967) employing ^{60}Co sources is the most widely used (WHO, 1975). The unit employs different sizes and shapes of uterine tubes and adjustable vaginal applicators (Fig. 1). The main feature of intracavitary therapy is the uniformity and adequacy of dose delivered to the paracervical region for various anatomical situations. Liversage *et al.* (1967) calculated the dose rate at point A for Cathetron therapy, assuming ideal Manchester loading. This paper deals with theoretical computations to study the effect of the size and shape of the uterine applicators and the separation of vaginal sources on the dose distribution in the paracervical region and in the sagittal plane passing through the bladder and the rectum, together with experimental measurements to verify the theoretical computations. The computed isodose distributions have also been compared with those of conventional Manchester loadings.

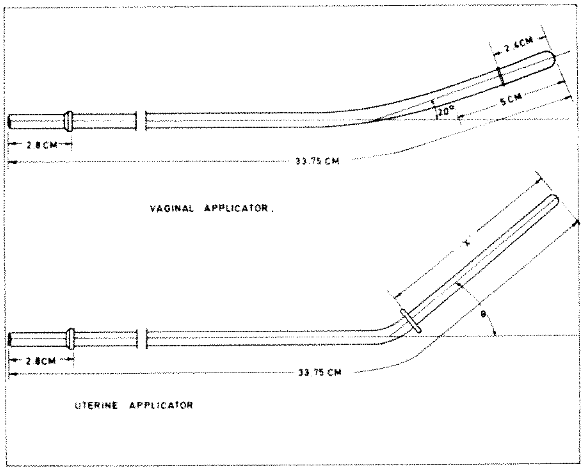


FIG. 1.

Stainless steel catheters used in Cathetron. Uterine tubes are available in 3 sizes, viz. X = 4.25, 6.25 and 8.25 cm, each with angles of anteversions θ of 0, 20, 30, 40 and 60 deg.

MATERIALS AND METHODS

The Cathetron unit employs catheters with a range of lengths of uterine tubes set at different angles in relation to the stem of the catheter. The lengths and angles are chosen in accordance with anatomical variations found in patients. The curvature of the ovoid catheters enables the radiotherapist to adjust the separation between the ovoid sources by manipulating the distance between the open ends of the catheters. The rigid ovoid catheters and thereby the longitudinal axes of the sources lie in or parallel to the coronal plane. The angle which the ovoid sources make with the plane of the uterine sources depends upon the anteversion of the uterine tube. Dose computations have been done for various loadings involving uterine tubes of lengths 4.25, 6.25 and 8.25 cm and angles of anteversions of 0, 20, 40 and 60 degrees. Separations between the centres of the vaginal sources of 2.0, 3.0, 4.0 and 5.0 cm and distances from the external os level of 1.0, 1.25 and 1.5 cm were considered. The activity of the sources considered for dosimetry are given in Table I.

Theoretical computations

For evaluation of exposure rate, the line source formula due to Sievert (1932) was used. As the expression is not valid for the paraxial region of a source element, the dose distributions in these regions were evaluated using a computer program (Jayaraman and Iyer, 1975) which involves three-dimensional integration taking into account the finite filtration at the ends of the sources. The effective filtration (μd) for the ^{60}Co γ rays was evaluated as

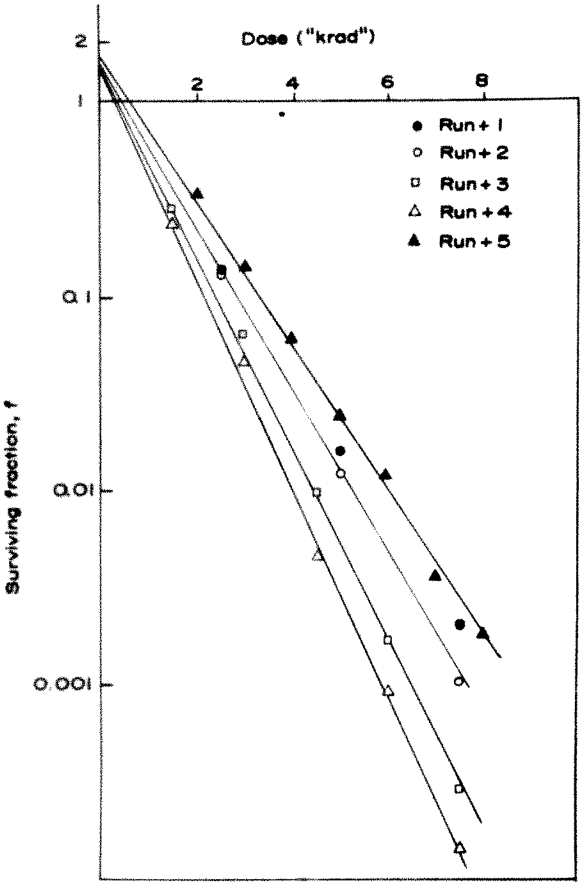


Fig. 2.

Survival curves for *E. coli* AB2463 recA suspended in buffer and irradiated on five separate occasions during development of the Fermilab neutron beam (67 MeV p on Be).

the USA quote total dose ($n+\gamma$), the Hammersmith D_0 in Table I is a corrected value to account for the 10% γ-ray contribution under the conditions of that experiment (Bewley, private communication). The data in Table I show the D_0 to be the same within experimental error ($\pm 5\%$) for the different fast neutron beams even though their mean energy varied from 4 to 25 MeV. Any variations in D_0 with mean neutron energy may well be masked by systematic errors in physical dosimetry and experimental error. Assuming the physical dosimetry of the neutron beams used is accurate to within $\pm 5\%$, the RBE (in terms of D_0 ratios) relative to several low LET sources is 0.95 ± 0.05. Thus the response of *E. coli* AB2463 recA can be used to intercompare dosimetry on fast neutron beams with mean energies in the range studied to an accuracy of $\pm 5\%$.

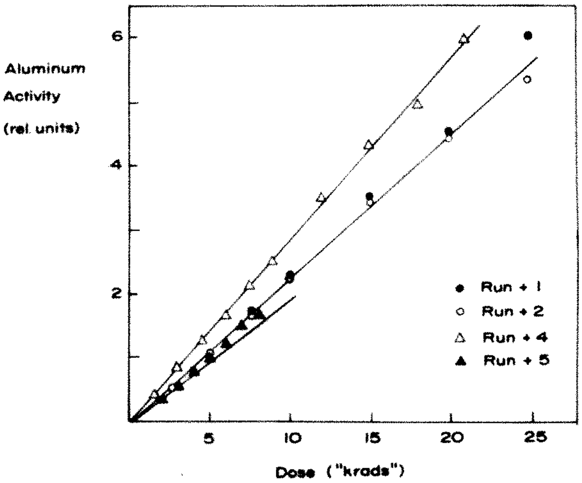


Fig. 3.

Measurements of aluminum activity as a function of nominal dose for Al discs irradiated in conjunction with *E. coli* AB2463 recA on four separate occasions with the Fermilab neutron beam (67 MeV p on Be).

In initial dosimetric and radiobiological studies with the fast neutron beam (67 MeV p on Be) at Fermilab during development of the beam it was decided to employ *E. coli* AB2463 recA as a dosimeter in addition to an air-filled, tissue-equivalent ionization chamber. Aluminum discs were used as neutron fluence monitors. Survival curves obtained on five such occasions are shown in Fig. 2. Clearly there were variations in the nominal dose on these different days and these were also reflected by the measurements of Al activity (Fig. 3). Day-to-day variations in physical dose measurements were later traced to faulty software in the computerized monitoring system. When survival was plotted against Al activity the points fitted well to a straight line (Fig. 4). Later experiments conducted at Fermilab (*e.g.* Fig. 1) indicated the RBE for Fermilab neutrons to be 0.95. It was then possible to calibrate the ^{24}Na activity of the Al discs to give the dose in rad.

Biophysical considerations

From studies of bacterial radiosensitivity as a function of LET it has been established that for LET$_\infty$ greater than 20 keV/μm the phenomenon of "overkill" occurs and radiosensitivity decreases (Munson *et al.*, 1967; Alper *et al.*, 1967). For the fast neutron beams considered in this study a considerable fraction (30–50%) of the absorbed dose is at LET values greater than 20 keV/μm (Bewley, 1968; Amols *et al.*, 1978; Weaver, private communication). In order that the RBE should be close to unity for these beams this organism must show a peak in radiosensitivity with LET at around 20 keV/μm. This is contrary to the indications of the limited

GERACI, J. P., THROWER, P. D., JACKSON, K. L., CHRISTENSEN, G. M., PARKER, R. G., and FOX, M. S., 1974. The relative biological effectiveness of fast neutrons for spinal cord injury. *Radiation Research*, *59*, 496–503.

GILMORE, S. A., 1972. Spinal nerve root degeneration in ageing laboratory rats: a light microscopic study. *Anatomical record*, *174*, 251–258.

INNES, J. R. M., and CARSTEN, A., 1961. Demyelinating or malacic myelopathy. *Archives of Neurology*, *4*, 190–199.

KOGEL, A. J. VAN DER, 1976. Radiation tolerance of the spinal cord: the dependence on fractionation and extended overall times. *IAEA Symposium on Radiobiological Research and Radiotherapy*, 1977, vol. I, 85–90.

1977a. Radiation tolerance of the spinal cord: time-dose relationships. *Radiology*, *122*, 505–509.

1977b. Radiation-induced nerve root degeneration and hypertrophic neuropathy in the lumbosacral spinal cord of rats: the relation with changes in ageing rats. *Acta Neuropathologica* (*Berl.*), *39*, 139–145.

KOGEL, A. J. VAN DER, and BARENDSEN, G. W., 1974. Late effects of spinal cord irradiation with 300 kV X rays and 15 MeV neutrons. *British Journal of Radiology*, *47*, 393–398.

MASTAGLIA, F. L., MCDONALD, W. I., WATSON, J. V., and YOGENDRAN, K., 1976. Effects of X-irradiation on the spinal cord: an experimental study of the morphological changes in central nerve fibres. *Brain*, *99*, 101–122.

MASUDA, K., REID, B. O., and WITHERS, H. R., 1977. Dose effect relationship for epilation and late effects on spinal cord in rats exposed to gamma rays. *Radiology*, *122*, 239–242.

WARA, W. M., PHILLIPS, T. L., SHELINE, H. E., and SCHWAYDER, J. G., 1975. Radiation tolerance of the spinal cord. *Cancer*, *35*, 1558–1562.

Book reviews

Bone marrow transplantation and other treatment after radiation injury. By H. Balner, (Martinus Nijhoff Medical Division—The Hague) pp. 83, 1977 (For The Commission of the European Communities), Dfl.27.50.

A generation ago there was much experimental activity to develop methods for chemical protection against the effects of ionizing radiation or to treat over-exposure if it occurred. Nuclear fission had newly become big business for peaceful and military purposes. Now we hear little about chemical protection: and laboratory or industrial accidents have been few (and military nuclear casualties fortunately nil). Thus most of us do not keep abreast of what is being done about the treatment of rare radiation casualties.

Originally the treatment of radiation casualties was also chemically orientated—the search for humoral or similar stimulators to recovery of cells of bone marrow. The successful treatment of lethally irradiated rodents in those early days was not due to magic biochemicals in administered bone marrow or spleen but to unpredicted successful transplantation. Some of the pioneer laboratories in these studies have pursued the investigations through dogs and monkeys to man. The objective has been not only the salvage of the rare radiation casualty but the development of bone marrow transplantation for the treatment of cases of aplastic anaemia, leukaemia and now "combined immunodeficiency diseases".

Dr. Hans Balner, the author of this 80-odd page monograph, has long been a member of one of these pioneer laboratories—TNO Rijswijk, Netherlands—and is Director of its Primate Center. He is thus perfectly equipped to review the subject. It could have been made a sensational story as for a Sunday newspaper, but rightly has been cast as a scientific review, complete with the dull bits and the still plenteous uncertainties. There are some 150 references, obviously not a complete bibliography, but a reasonable selection to give the studious reader a good start to any line he wishes to pursue. Inevitably, particularly in clinical transplantation for the diseases listed above, there have been later reports updating the information supplied to the end of 1976.

J. A. F. LOUTIT.

Nuclear medicine: clinical and technological bases. By J. T. Andrews, and M. Jean Milne, pp. 468, 1977 (John Wiley, Chichester; New York), £18·75.

This book is based on a three year course of lectures for technicians (or "nucleographers"), and aims to give a clear understanding of the principles of the subject as a basis for a good standard of practical procedure. After a good introductory chapter on the role of the technician in nuclear medicine, the first half of the book describes each system of the body and the relevant radioisotope procedures. This integrated approach is generally successful but occasionally confusing. The style is didactic and thorough, although rather pedantic at times. There are a number of points which one hopes will be tidied up in a subsequent edition. No mention is made of the hazards associated with iron hydroxide particles or of lung scanning in patients with diffuse pulmonary hypertension, a factor of some importance as it is envisaged elsewhere in the book that the technicians themselves may administer the radiopharmaceuticals. Few would agree with the optimistic view of the value of pancreas scanning and the quoted radiation dose to the liver from ^{75}Se selenomethionine (page 158) is incorrect. Certain sections are somewhat dated, *e.g.* the emphasis on ^{85}Sr in the chapter on bone, and although ^{67}Ga is mentioned several times in connection with tumour localization, there is no reference at all to its value in abcess localization.

The second half of the book contains detailed technical descriptions of the different tests and the physical principles underlying them. This section will be useful for reference and will serve as a model for the procedure sheets which should be available in any department to ensure a high and consistent standard of work.

This book fills a gap in the literature and will be a useful addition to any departmental library, particularly in those concerned with the training of technicians. It will not, in my view, have much appeal to clinical and scientific staff, as suggested in the foreword, but it will provide valuable and at times simulating reading for technicians and radiographers, not least if it occasionally provokes the question "why do we do that differently?".

E. P. WRAIGHT.

designed and fabricated in this laboratory. As the measurements were extended over several days, the day-to-day variation of the sensitivity of the reader was checked using phosphor exposed to a standard dose. The average TL response in terms of mV/mg was evaluated for each dosimetric point and normalized to the response of the standard phosphor. The phosphor was calibrated by exposure to known doses of γ rays from a ^{60}Co teletherapy machine.

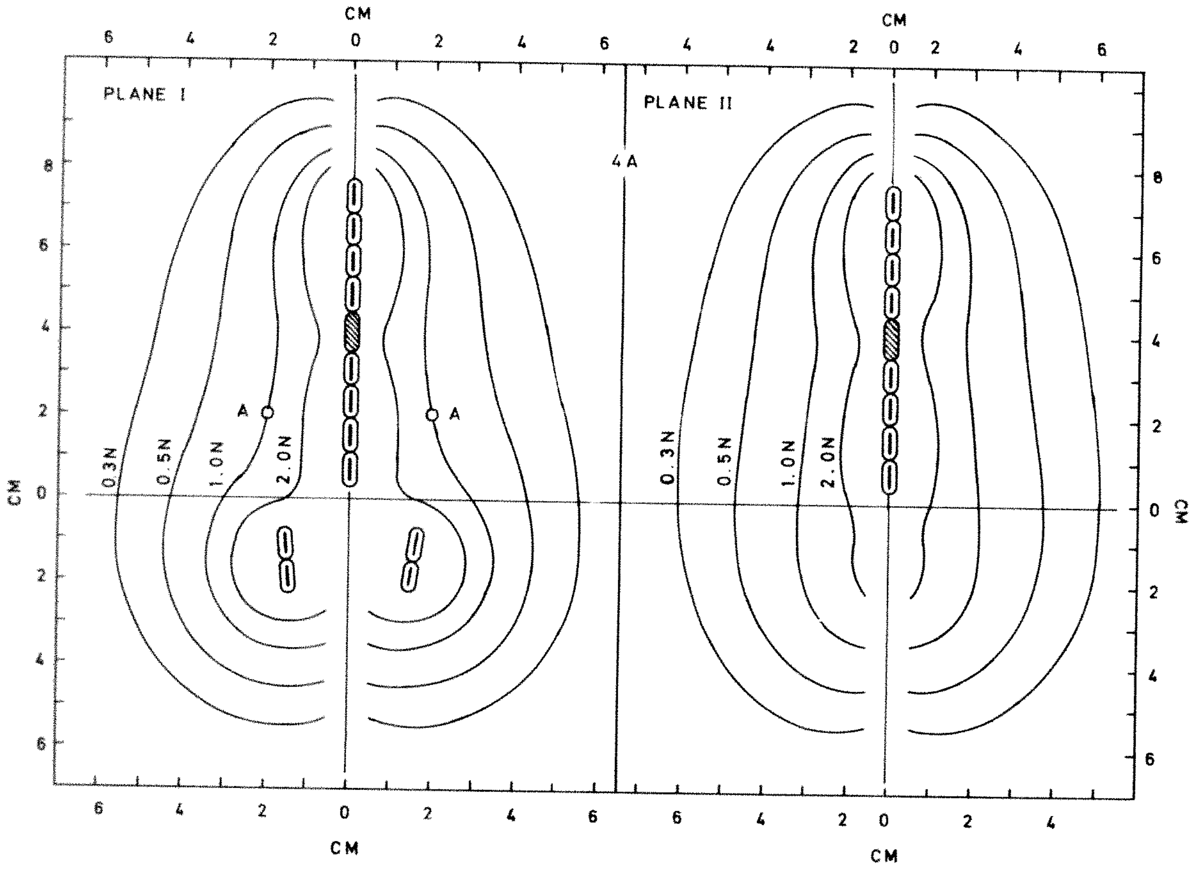
Comparison with Manchester technique

An ideal Manchester loading using medium size uterine tube and large vaginal ovoids is compared with a Cathetron loading in Fig. 3 for a straight uterus. The total active length and the relative activities of the uterine sources are quite comparable in the two cases. In the Manchester loading the plane of the ovoid sources lies perpendicular to the uterine sources whereas all sources lie in the same plane for the Cathetron loading. Further, the relative activity of the Cathetron ovoid source pencils is about 12.5% less than that of the Manchester ovoids.

Dose computations have been done for the above loadings, to compare the isodose distributions. The specific γ ray constant of radium γ rays was considered as 9.068 R cm^2 mCi^{-1} h^{-1} (NCRP, 1974) and the effective μd as 0.1864 (Young and Batho, 1964) for a filtration of 1.0 mm Pt 10% Ir. The isodose distributions thus obtained are given on the left of Fig. 6 (planes Ia and IIa) and those derived for Cathetron ovoid source pencils of 12.5% higher activity on the right half (planes Ib and IIb).

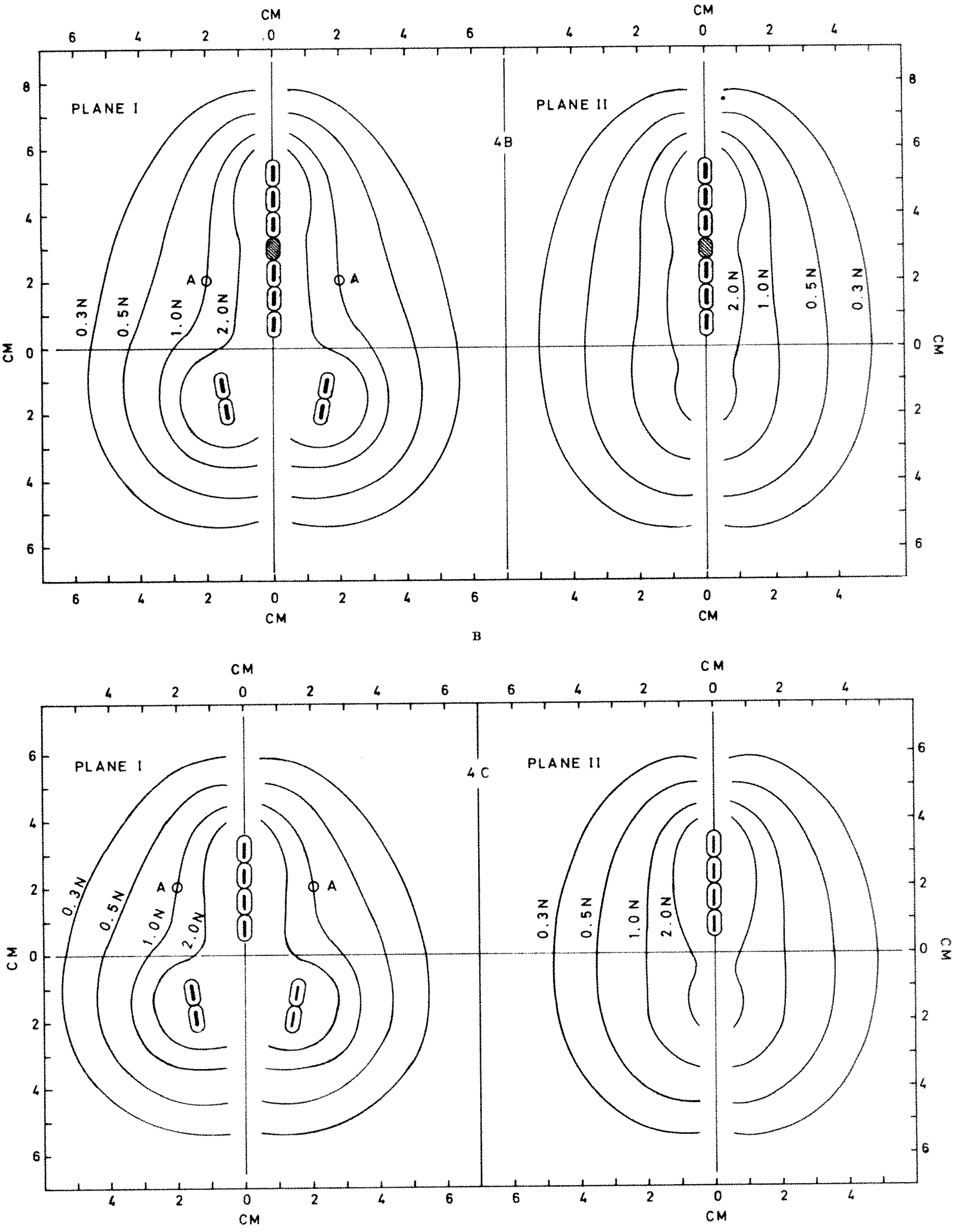
RESULTS AND DISCUSSION

Tables IIA–IID give the dose rates at points A and B for the various loadings employed in Cathetron therapy. It can be seen from Table IIA that the variation of dose rate at point A is negligible for the three sizes of uterine tube. Since the relative position of point A does not vary with the anteversion of the uterine tube (Meredith, 1967), the contribution



A

FIG. 4.


CM
6 4 2 0 2 4 6
PLANE I
4B
PLANE II
A
A
0.3N
0.5N
1.0N
2.0N
8 6 4 2 0 2 4 6
CM
4 2 0 2 4
CM
PLANE I
4C
PLANE II
A
A
0.3N
0.5N
1.0N
2.0N
6 4 2 0 2 4 6
CM

B

C

FIG. 4.

THEORY OF RECIPROCITY LAW FAILURE

Reciprocity law failure is described in many textbooks, *e.g.* by Mees and James (1962) and Herz (1969). Photographic emulsions are most sensitive when the intensity of the exposing radiation is such that an exposure time between 0.01 and 10 seconds is required to produce a medium film density. Decreased sensitivity may occur at higher or lower intensities. For technical reasons only the low-intensity reciprocity law failure needs to be considered for medical radiography. Indirectly it is accounted for by distinguishing between time-scale and intensity-scale sensitometry. Some understanding of the processes occurring during the blackening of a silver halide film is necessary. According to the model described by Gurney and Mott (1938), so-called sensitivity specks, *i.e.* silver sulphide impurities of the AgBr grain, are essential for latent image formation. A photon absorbed in the grain produces photoelectrons, which in turn produce slow electrons. These electrons can move freely in the conduction band until they are trapped in a sensitivity speck. The sensitivity speck becomes negatively charged and attracts positive silver ions from interstitial sites. The (neutral) silver speck initiates the reduction of the AgBr grain to metallic silver during development, but is not stable below a certain size. With direct X-ray exposure a large enough silver speck is produced by a single photon. With visible-light exposure, on the other hand, a number of photons need to be absorbed. If the time between two subsequent absorptions is too long

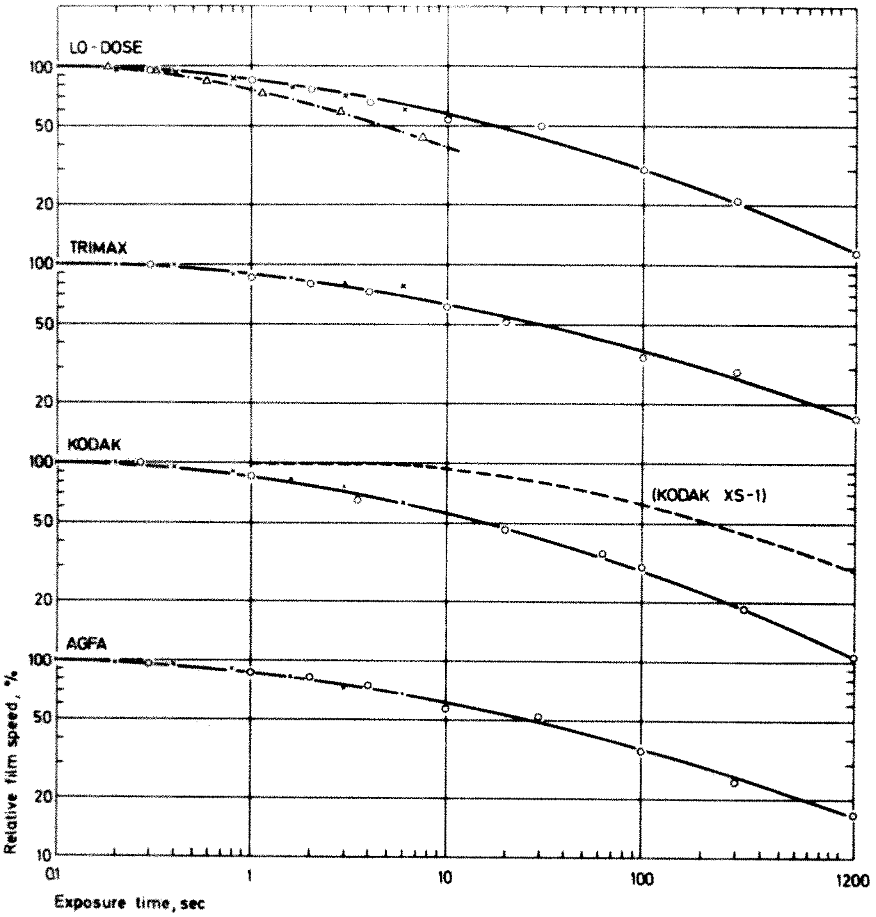


FIG. 1.

Relative speeds of four film/screen combinations used in mammography versus exposure time. Measurements were carried out using X rays (crosses) and visible light (circles). Also included are measurements on a double-coated film used in general radiology (dashed line), and a curve (triangles) based on data published by Friedrich and Weskamp (1976) and shown in the uppermost section.

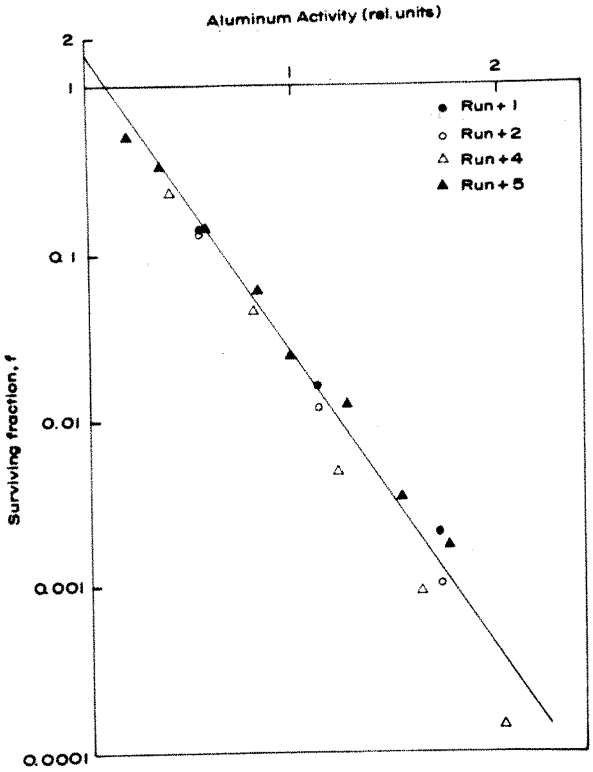


FIG. 4.

Surviving fraction plotted against Al activity measurements (combining data of Figs. 2 and 3).

data for *E. coli* AB2463 recA published by Munson *et al.* (1967) which indicate a flat response followed by overkill. Clearly it would be desirable to conduct a carefully controlled study of the response of this organism as a function of LET∞.

Included in Table I is a value of D_0 measured with the fission neutron beam from the Janus Reactor by Peak and Ainsworth (1973). This D_0 is considerably greater than that measured on the higher energy fast neutron beams indicating a large amount of "overkill" in bacteria with fission neutrons. This is consistent with calculations which estimate that about 90% of the absorbed dose is at LET values greater than 20 keV/μm for fission neutrons (Bewley, 1968).

ACKNOWLEDGMENTS

The encouragement and advice of Drs. L. Cohen, M. Awschalom, D. Young, and Mr. A. Jones (all of Cancer Therapy Facility, Fermilab), Dr. F. Kuchnir (University of Chicago), Dr. J. Ovadia (Michael Reese Hospital), and Dr. T. Alper (Gray Laboratory) is gratefully acknowledged. The physicists and biologists at the various neutron facilities are thanked for their co-operation. Partial support for this work came from Public Health Service Grant No. 1 PO 1 CA 18081-01.

REFERENCES

ALPER, T., 1971. In *Biophysical aspects of radiation quality*, IAEA-SM-145-1, pp. 171–183 (Vienna).

AMOLS, H. I., DICELLO, J. F., AWSCHALOM, M., COULSON, L., JOHNSEN, S. W., and THEUS, R. B., 1978. Physical characterization of neutron beams produced by photons and deuterons of various energies bombarding beryllium and lithium targets of several thicknesses. *Medical Physics 4*, 486–493.

ATTIX, F., and ROESCH, W. C. (eds.), 1968. *Fundamentals of Radiation Dosimetry*, Vols. I, II, III (Academic Press, N.Y./London).

BEWLEY, D. K., 1968. Calculated LET distributions of fast neutrons. *Radiation Research*, *34*, 437–445.

1970. Fast neutron beams for therapy. *Current Topics in Radiation Research*, *6*, 249–292.

COHEN, L., and AWSCHALOM, M., 1976. The cancer therapy facility at the Fermi National Accelerator Laboratory, Batavia, Illinois: a preliminary report. *Applied Radiology*, Nov.–Dec., 51–60.

MUNSON, R. J., NEARY, C. J., BRIDGES, B. A., and PRESTON, R. J., 1967. The sensitivity of *Escherichia coli* to ionizing particles of different LET's. *International Journal of Radiation Biology*, *13*, 205–224.

PARNELL, C. J., and BEWLEY, D. K., 1976. Dosimetry of the fast neutron beam produced by the MRC cyclotron. *British Journal of Radiology*, *49*, 298.

PEAK, M. J., and AINSWORTH, E. J., 1973. Inactivation of ultra-violet sensitive mutants of *Escherichia Coli* by fast neutrons. Argonne National Laboratory Ann. Report (ANL-8070), pp. 195–196.

Book review

Erkrankungen des Magens (*Diseases of the Stomach*). Contributions by M. Classen, W. Dolle, W. Frik, R. Herzer, W. Holthusen, G. Kieninger, B. Kommerell, L. Koslowski, D. Meyer, D. Schoen, K.-Fr. Sewing, H. J. Sielaff, and R. Siewert, pp. 142., illus, 1977 (Georg Thieme Verlag, Stuttgart), DM.54.

This is a multidisciplinary review of the diseases of the stomach written with the radiologist in mind, to keep him up to date with the examination of the stomach in adults and infants, using radiological endoscopic and radioisotope techniques. There are chapters on the physiology and pathological anatomy of the stomach, on the medical and surgical treatment of gastric lesions and on post-operative appearances. The book brings together much old and new information from a fast expanding field of knowledge. It will be of great value to the practising radiologist. There are good lists of references. A very useful book.

G. M. STEINER.

ACKNOWLEDGMENTS

The authors wish to acknowledge the sincere assistance and co-operation of Professor M. S. Dvivedi and other staff members of the Radiotherapy Department, Cancer Hospital, Indore in making the Cathetron unit available to us. Thanks are also due to Professor C. A. Joslin for going through the manuscript of this paper. We are grateful to Mr. S. Jayaraman and Mr. P. S. Viswanathan for helping in this work.

EDITORIAL NOTE

The following additional figures are available from the authors on request:
Isodose distributions normalized at point A in the paracervical (plane I) and sagittal (plane II) planes for varying length of uterine tube, angle of anteversion and separation of vaginal sources, for a fixed distance from the level of the external os.

REFERENCES

O'Connell, D., Joslin, C. A., Howard, N., Ramsey, N. W., and Liversage, W. E., 1967. The treatment of uterine carcinoma using the Cathetron. Part I—Technique. *British Journal of Radiology*, *40*, 882–886.

Jayaraman, S., and Iyer, P. S., 1975. Dose distribution in the paraxial regions of cobalt-60 and caesium-137 brachytherapy line sources. *Proceedings of a conference on Biomedical Dosimetry*, *IAEA-SM-193/28*, 327–334.

Johns, H. E., and Cunningham, J. R., 1971. *Physics of Radiology*, 3rd edn, pp. 736 (Charles C. Thomas, Springfield, Illinois).

Liversage, W. E., Martin-Smith, P., and Ramsey, N. W., 1967. The treatment of uterine carcinoma using the Cathetron. Part II—Physical measurements. *British Journal of Radiology*, *40*, 887–894.

Meisberger, L. L., Keller, R., and Shalek, R. J., 1968. The effective attenuation in water of the gamma rays of gold-198, iridium-192, caesium-137, radium-226 and cobalt-60. *Radiology*, *90*, 953–957.

Meredith, W. J., 1967. *Radium Dosage: The Manchester System*, 2nd edn, pp. 47–49 (E. & S. Livingston, Edinburgh).

NCRP, 1974. Specification of gamma-ray brachytherapy sources. *Report No. 41*.

Santhamma, A. V., and Das, K. R., 1978. The determination of total activity and its distribution in Cathetron source pencils. *Strahlentherapie*. (in press).

Sievert, R. M., 1932. Eine methods zur Messung von Rontgen; Radium—und ultra-strahlung nebst einigen unterschungen uber die Anwendbarkeit derselben in der physik und er Medizin. *Acta Radiologica, Supplement XIV*.

WHO, 1975. *Report of an IAEA/WHO Seminar on Afterloading Techniques in Radiotherapy*, India RAD/75.3, p. 63.

Young, E. J., and Batho, H. F., 1964. Dose tables for linear radium sources calculated by an electronic computer. *British Journal of Radiology*, *37*, 38–44.

Book review

Radiography in Obstetrics. By A. Stirling Fisher and J. G. B. Russell, pp. vii+81, illus. (Butterworths, London), £2·65.

This book is a new edition of "A place for Radiography in Obstetrics" written in 1975 by Dr. J. Blair Hartley and Miss A. Stirling Fisher. It is written in clear concise and simple terms and is primarily for the guidance of radiographers. There is little change in the contents since the first edition although an attempt has been made to introduce superficial comments on the change in the place of obstetric radiography in the light of newer imaging techniques, especially diagnostic ultrasound.

The main value of this book lies in the detailed description of the technique of radiography of the pregnant abdomen and particularly the Manchester method of pelvimetry, and in this respect only, is of interest to radiologists and obstetricians. Although with the availability of sophisticated ultrasonic equipment there has been a marked reduction in the number of cases referred for X-ray examination, it is nevertheless essential that radiographers and radiologists should have a knowledge of basic obstetric radiography techniques. This book serves the purpose adequately but has little to offer beyond this remit.

E. Barnett.

1978, *British Journal of Radiology*, *51*, 515–523

Radiation damage to the rat spinal cord: the effect of single and fractionated doses of X rays

By Ann White, PhD., B.Sc., and Shirley Hornsey, D.Sc.

MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W12 OHS

(Received September, 1977 and in revised form January, 1978)

ABSTRACT

The tolerance of the rat lumbar spinal cord to single and multiple doses of X irradiation has been studied using paralysis of the hind legs as the endpoint. The paralysis, which has an acute onset progressing from the first symptoms to full paralysis within two to three days, occurs within one year post-irradiation. Dose/effect relationships were estimated at one year. Experiments which were designed to study the effect of varying the overall treatment time between two equal doses of X rays showed that a large amount of recovery from irradiation damage occurred during the first 24 hours after irradiation (D_2–D_1 at 24 hours was 950 rad). No further recovery took place for another 15 days but at 32 days another wave of recovery seemed to be in progress (D_2–D_1 at 32 days was 1250 rad).

The effect of varying the number of fractions independently of the overall treatment time was investigated. The tolerance of the cord increased rapidly as the number of fractions given in a six-week period was increased from four to 30. The slope of a Strandqvist-type plot of this data was about 0.4. The data for the spinal cord have been compared with similar data for late damage in the mouse lung.

The latent period between irradiation and the onset of paralysis was also investigated. At high doses, when the probability of paralysis occurring was great, the latent period was independent of the dose. At lower doses which gave rise to a lower incidence of paralysis, the latent period was inversely related to the dose.

A second type of paralysis occurred later than one year after irradiation. This had a very protracted development and occurred in unirradiated as well as irradiated animals.

The spinal cord is sometimes unavoidably included in the treatment fields used in radiotherapy. This can result in the development of myelopathy after periods ranging from a few months to several years. The response of normal nervous tissue is thus an important factor limiting the dose of irradiation to which some tumours can be exposed. It is therefore desirable to determine the tolerance of the spinal cord to irradiation and particularly to determine the relationships between limiting dose and fractionation.

The dose of irradiation which normal tissues can tolerate varies with the number of fractions (N) in which the dose is given and with the overall treatment time (T). Ellis (1969) has proposed that the relationship between the dose which a tissue will tolerate, the number of fractions and the overall treatment time is described by the formula

$$\text{tolerance dose} \propto N^{\alpha}\, T^{\beta}$$

From clinical data and from experiments on pig skin (Fowler, 1965), Ellis calculated the exponents of N and T to be 0.24 and 0.11 respectively for irradiation with X rays. For lung damage using death from radiation pneumonitosis as the endpoint, Field *et al.* (1976) have calculated the exponent of T to be 0.07 while that of N appears to vary with the number of fractions given, being 0.39 for one to eight fractions and 0.25 for eight to 30 fractions.

Early studies of the effects of irradiation on the spinal cord involved the use of single, large doses of irradiation (Innes and Carsten, 1961; Carsten and Zeman, 1966; Geraci *et al.*, 1974). Recent experiments by van der Kogel (1977a and b) have shown that the tissue tolerance curve for late damage to the spinal cord from one to twenty fractions has a slope of about 0.44. In his experiments the tissue tolerance was unaffected by variations in the overall treatment time unless this was extended to periods greater than eight weeks.

The experiments described in this paper were designed to investigate the effects of varying the number of fractions of X rays and the overall time in which they are given on the development of damage to the lumbar cord of rats. Also included are some preliminary data on the cervical cord.

Van der Kogel (1977b) has suggested that there are two distinct time periods over which myelopathy develops in the rat cord. The first phase occurs after latent periods of four to seven months after irradiation: the second phase occurs after latent periods of more than one year. We have limited our observations on the dose-effect relationship to the first acute phase but have included some data on the second phase.

In general our results on the first phase confirm and extend the findings of van der Kogel but they do differ in a few specific points.

METHODS

The spinal cords of three-month-old male CFHB rats (Anglia Laboratory Animals) were irradiated in the lumbar region or in the cervical region with X rays generated by a Marconi 250 kV X-ray set, at a dose rate of 200 rad/min. The filtration used was 0.3 mm Cu and 1 mm Al giving a half-value layer of 1.35 mm Cu. To avoid damaging the gut or the oesophagus a lateral beam was used. The animals were lightly anaesthetized with sodium pentobarbitone (30 mg/kg intraperitoneally) and placed, dorsal surface uppermost, on a Perspex platform in which a hole was cut to allow the gut to fall out of the irradiation field. The irradiation field was restricted to the lumbar or cervical region by means of a hole 4.0 cm square cut in a 3 mm thick lead plate which was placed as close as possible to the rat. The length of cord irradiated was further limited to 2.5 cm of the lumbar cord (vertebrae 3–5) and to 1.5 cm of the cervical cord, by means of lead saddles which could be placed over the rats. Radiographs were taken to determine the precise location of the fields irradiated. The dose to the cord in both regions was determined by placing lithium fluoride capsules inside the vertebral column of a dead rat.

The lumbar cord received either a single dose of X rays, two equal doses of X rays separated by varying periods of time (one, four, eight, 16 or 32 days) or four, eight, 15 or 30 equal doses of X rays over a six-week period. The irradiations were done in three batches and on each occasion the single dose treatment was repeated thus enabling comparison to be made between all irradiated rats. The cervical cord received either a single dose or eight equal doses in a six-week period. Eight or ten rats were irradiated at each dose.

Following irradiation the animals were examined weekly until the first signs of cord damage occurred in that batch of animals; they were then examined daily from Monday to Friday. Irradiation of the lumbar spinal cord of rats with sufficiently high doses, *i.e.* single doses of over 2000 rad of 250 kV X rays, results in paralysis of the hind legs which develops from about three months to one year after irradiation (van der Kogel and Barendsen, 1974). Damage to the lumbar region was detected by lifting rats by their tails. In a normal rat this elicits an extension reflex of the hind legs. A weak extension reflex was the first sign of radiation injury to the cord. Later the leg muscles became atrophied and the

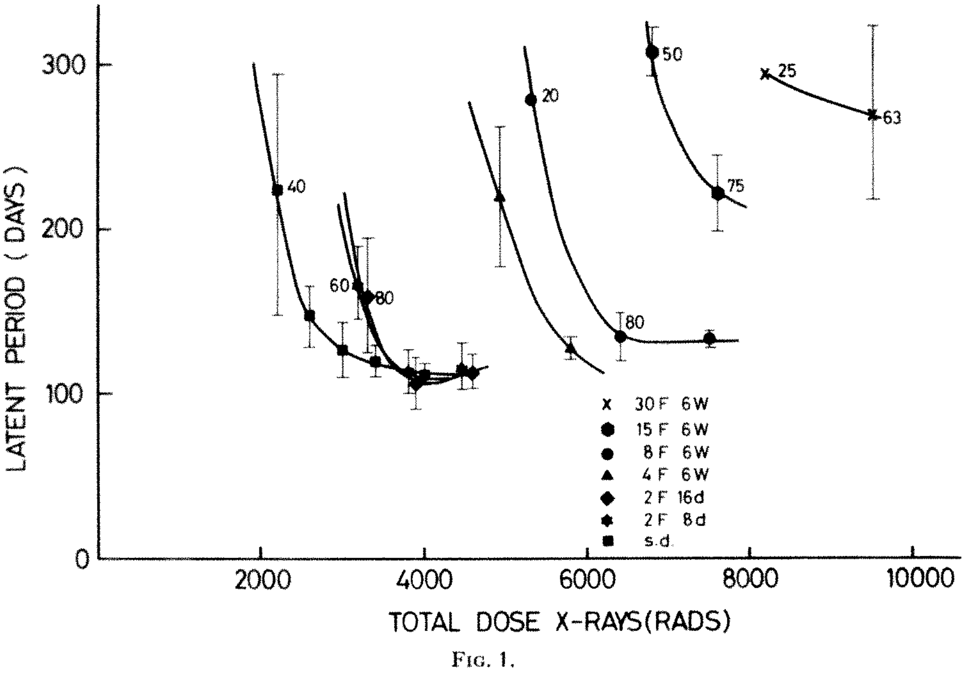


Fig. 1.

Relationship between total dose and latent period for the development of partial paralysis following exposure of the lumbar spinal cord to:—

A single dose of X rays	■
Two equal doses separated by 16 days	◆
Two equal doses separated by eight days	✱
Four equal doses in six weeks	▲
Eight equal doses in six weeks	●
15 equal doses in six weeks	•
30 equal doses in six weeks	X

The latent period is calculated from the first exposure for the fractionated schedules. Numbers next to points indicate the percentage of rats which became paralysed at that particular dose. If no figure is given there was a 100% incidence of paralysis.

animals were mildly ataxic. This was taken as the endpoint of the experiment. A few rats which were allowed to survive beyond this stage became completely paralysed in the hind legs and were found to have distended urinary bladders on post-mortem examination. Ataxia and weakness of the front legs was taken as the endpoint for the cervical irradiations.

Statistical treatment of results

The dose of X rays which produced ataxia and loss of the extension reflex of the hind legs in 50% of the rats (ED_{50}) was derived graphically for each treatment. Since most of the dose-effect curves had only one point between a zero and a 100% effect it was not possible to use probit analysis to determine the errors of the ED_{50} measurements. Instead the standard error of the proportion of rats paralysed at a particular dose was obtained using the formula $\text{s.e.} = \sqrt{\frac{p(1-p)}{n}}$ where p is the proportion of affected animals and n is the number of animals in the group. Curves were then drawn by eye to envelope the error bars about each individual dose on each dose-effect curve and the variance about the ED_{50} point on the curves was thus read off. The number of animals which had to be killed due to the development of disease or tumours or which died of other causes was deducted from the original number of animals in each group before calculating the percentage of rats which became paralysed at each dose.

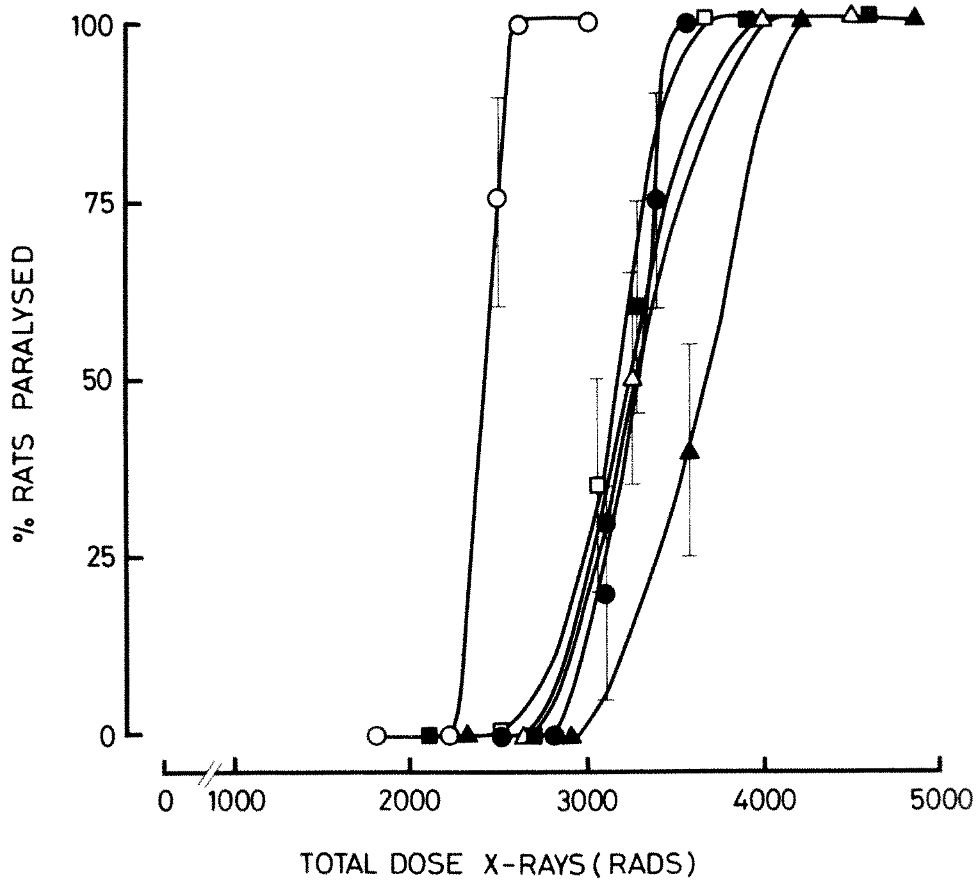


Fig. 2.

Dose-effect curves for:
(1) A single dose of X-rays to the lumbar cord ○ (2) Two equal fractions in
(a) 24 hours ● (results of two experiments combined)
(b) 4 days □
(c) 8 days △
(d) 16 days ■
(e) 32 days ▲

Results

Latent Period

The relationship between the dose of 250 kV X rays to the spinal cord and the latent period for development of partial paralysis is shown in Fig. 1 which gives the results after single doses and after two, four, eight, 15 or 30 equal fractions of radiation.

It can be seen that paralysis following irradiation of the lumbar cord appears after a minimum period of between 100 and 140 days. Following doses of radiation which are large enough to give rise to a high probability of paralysis, the latent period appears to be independent of the dose given. It is also independent of the fractionation schedule employed, being of similar duration following a single dose, two equal doses separated by different intervals of time, and four or eight equal doses in six weeks.

At the lower doses used for each fractionation schedule the mean latent period for those animals showing paralysis was longer, indicating that at doses causing a low incidence of paralysis the latent period was inversely related to dose. After the highest doses given in 15 and 30 fractions less than 100% of rats had become paralysed even at one year after irradiation. The latent period was, therefore, much longer; no rats succumbed to spinal cord damage within 200 days after irradiation with 15 or 30 fractions.

TABLE I

ED_{50} following two equal doses of X rays separated by varying times

Treatment	ED_{50} (rad) ± 2 × variance
Single dose	2400 ± 80
2F/1d 1st expt.	3350 ± 100
2nd expt.	3300 ± 100
2F/4d	3200 ± 240
2F/8d	3250 ± 200
2F/16d	3250 ± 200
2F/32d	3650 ± 200

Overall treatment time (T)

The proportion of animals showing ataxia and loss of the extension reflex of the hind limbs at six months after treatment was plotted against total dose for animals given two equal doses of X rays separated by periods of time ranging from one day to 32 days (Fig. 2). The effect of single doses of X rays is shown for comparison. The doses of X rays which produced paralysis of the hind legs in 50% of the rats (ED_{50}) were derived from these curves and are given in

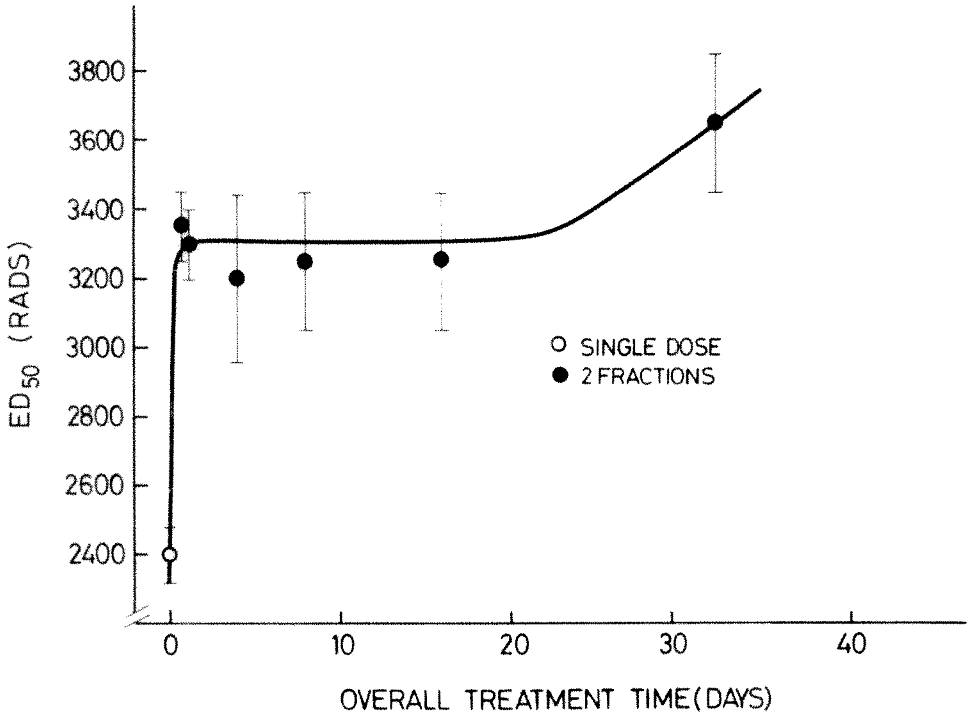


Fig. 3.

Relationship between ED_{50} and overall treatment time. Bars show variance.

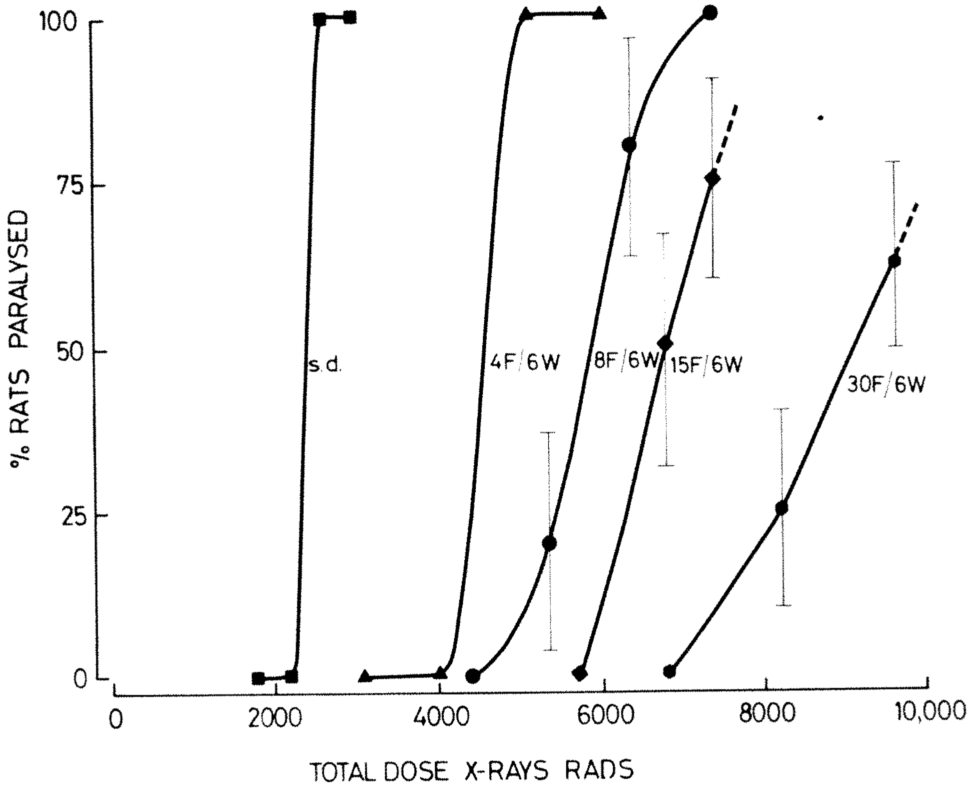


FIG. 4.

Dose-effect curves for a single dose and for four, eight, 15 and 30 equal doses of X rays to the lumbar cord in six weeks.

TABLE II

ED_{50} FOLLOWING FOUR, 8, 15 OR 30 EQUAL DOSES OF X RAYS IN SIX WEEKS

Treatment	Region	ED_{50} (6 months) (rad) ±2 × variance	ED_{50} (1 year) (rad) ±2 × variance
Single dose	Lumbar	2400 ± 200	2400 ± 200
4F/6W	Lumbar	5000 ± 400	4600 ± 500
8F/6W	Lumbar	6200 ± 400	5900 ± 250
15F/6W	Lumbar	—	6800 ± 400
30F/6W	Lumbar	—	9200 ± 600
Single doses	Cervical	2400 ± 200	—
8F/6W	Cervical	6300 ± 400	—

Table I. ED_{50} values obtained for treatments involving two doses of X rays using either the date of the first dose or the mid-point of the fractionated series were identical. Unfortunately, these animals contracted a lung infection and had to be killed at about nine months after irradiation and so no data are available on them at later times. However, very few rats had succumbed to spinal cord damage between six and nine months after irradiation.

The ED_{50} values from Table I are plotted against overall treatment time in Fig. 3. This shows that considerable recovery from radiation damage occurs during the first 24 hours after irradiation. $(D_2–D_1)$ at 24 hours is 950 rad. There seems to be no additional recovery from the damage inflicted by the first dose of irradiation during the next 15 days. However, at 32 days a second wave of recovery seems to be under way for $(D_2–D_1)$ increases to 1250 rad between 16 and 32 days. Increasing the overall treatment time from one to 16 days, therefore, gives little sparing of the lumbar cord. With treatment times longer than 16 days the total dose of irradiation which the cord will tolerate increases. Preliminary observations on the cervical cord appear to support these results and will be reported elsewhere.

Number of fractions N

The ED_{50} values at six months and one year after irradiation were derived graphically in the same way as for the two fraction experiment. The dose-effect curves for the lumbar cord at one year after irradiation are shown in Fig. 4 and the ED_{50} values are given in Table II. Only six month values are available for the cervical cord at present. No animals subjected to 15 or 30 fractions became paralysed within six months although doses up to 9600 rad in 30 fractions and 7500 rad in 15 fractions were given.

The variation in ED_{50} with increasing number of fractions is shown graphically in Fig. 5. The slope of a linear isoeffect curve drawn between one and 30 fractions is 0.40 and is in quite good agreement with that obtained by van der Kogel (1977a) from one to 20 fractions (0.44). The slope of a line drawn between four and 30 fractions both given in six weeks and therefore independent of time gives an estimate of the exponent of N in the Ellis formula and is approximately 0.35.

Fate of rats allowed to survive for 18 months after irradiation

Animals which received 15 or 30 fractions of X rays to the lumbar cord and did not become paralysed within one year of irradiation were allowed to survive for a further six months. During this time, however, some died of unknown causes or had to be sacrificed either because they developed tumours in the irradiated region or because they developed severe respiratory disease. Of the total number of animals which received 15 or 30 fractions 5% were found dead from unknown causes, 10% developed a respiratory infection which was so severe that they had to be sacrificed and 10% developed tumours in the irradiated region. In addition many animals suffered from a more mild chronic respiratory infection.

Four irradiated animals appeared to develop myelopathy between 12 and 18 months. This was characterized by muscular atrophy and weakness leading to ataxia of the hind legs but the paralysis developed much more slowly than that which occurred at latent periods of less than one year. However, as the rats became older and more diseased it became difficult to distinguish between weakness due to radiation damage and that due to disease. Two unirradiated (control) rats became very thin and showed muscular atrophy and weakness of the back legs similar to that seen in the irradiated rats, though this must have been due to the combined effects of disease and aging.

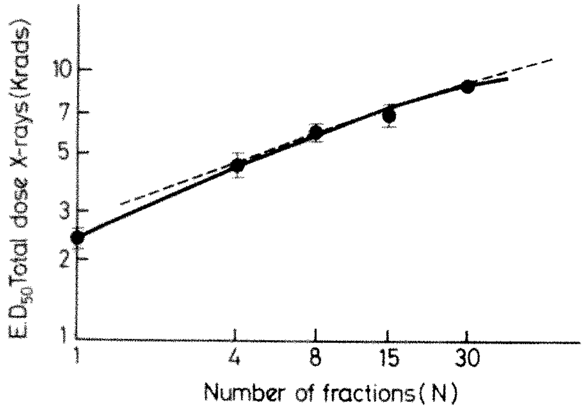


FIG. 5.

Log ED_{50} as a function of log number of fractions. Bars show variance.

DISCUSSION

The latent period between administration of X rays to the lumbar spinal cord and development of acute ataxia and partial paralysis appears to have a minimum of 100–140 days at high doses regardless of whether the dose is given in a single exposure or fractionated. The mean latent period in animals developing paralysis after lower doses increases with a decrease in dose. A similar relationship between dose and latent period has been reported by van der Kogel and Barendsen (1974) and more recently by Masuda *et al.* (1977). Van der Kogel suggests that the minimum latent period is probably related to the turnover rate of the Schwann cell population of the spinal roots which appears to be the most radiation sensitive cell type in the lumbar region.

It is difficult to come to any firm conclusion about the development of irradiation damage to the lumbar cord between 12 and 18 months since so few animals showed any neurological signs during this period and since so many animals were lost due to other causes. However, we believe that the syndrome of muscular atrophy and weakness of the hind legs at these later times is caused by a combination of the effects of irradiation and ageing, probably exacerbated by the development of disease. Both Gilmore (1972) and van der Kogel (1977a) have reported degenerative lesions, similar to those seen in irradiated animals, in the spinal roots of unirradiated but ageing rats. Although it would be interesting, in view of the long time course of the development of paralysis in patients, to study radiation damage in the cords of rats at longer times after irradiation, the lifespan (approximately 1½ to 2 years) of this strain of rat and the development of diseases do not permit this.

Time and Dose Fractionation

The mechanisms underlying the sparing of the spinal cord with increasing overall treatment time or dose fractionation are not known. The first rapid phase of recovery within 24 hours of irradiation may reflect Elkind repair of sublethal damage. The large value for (D_2–D_1) of 950 rad obtained for damage to the lumbar cord indicates that the recovery from accumulated sublethal damage is considerable and we might expect this to be reflected in a rather large exponent for the N factor. The slope of a linear isoeffect curve from one to 30 fractions is 0.40 and the correction for overall treatment time may be quite small. This does suggest a large value for the exponent of N. In Fig. 6 the total dose for fractionated treatments divided by the single dose for the same response has been plotted against the number of fractions to compare the present results for spinal cord with those previously reported for late damage in lung, a tissue with a relatively low cell turnover for which the exponents of N and T have been well defined experimentally. Also plotted in Fig. 6 are observations made on the cervical cord up to six months after irradiation (see Table II) and the observations of van der Kogel (1977a and b) on lumbar and cervical cord.

The response of cord and lung to X rays is similar at less than eight fractions but the cord response appears to depart from the lung response when more than eight treatments are given. A line of slope about 0.4 would give a good fit to all the cord data from one to 30 fractions but only fits the lung data between one and eight fractions: from eight to 30 fractions a line with a less steep slope (0.25) gives a better fit. This indicates that the sparing effect of fractionation may be greater for damage to the cord than to the lung and this shows most clearly at small fraction sizes and larger numbers of fractions.

The second phase of recovery seen in the split dose experiments after 16 days could be due to replacement of radiation-damaged cells by repopulation. In the lumbar region of the spinal cord the cells most vulnerable to irradiation appear to be the Schwann cells in the spinal roots. The only type of lesion seen in histological sections prepared from the cords of rats paralysed by irradiation was the demyelination of the roots. The Schwann cells of peripheral axons are not thought to divide at all in adult rats (Cavanagh, 1968). Schwann cells in the roots may differ in this respect, or their division may be triggered off by the damage to the cord inflicted by irradiation. Although the rats show no physical signs of damage to the cord until they become paralysed at about three months after irradiation, evidence has recently been produced by electron microscopy to show that demyelination and remyelination of axons in the spinal cord occurs at periods as short as four weeks after irradiation with single doses of X rays as low as 1000 rad (Mastaglia *et al.*, 1976).

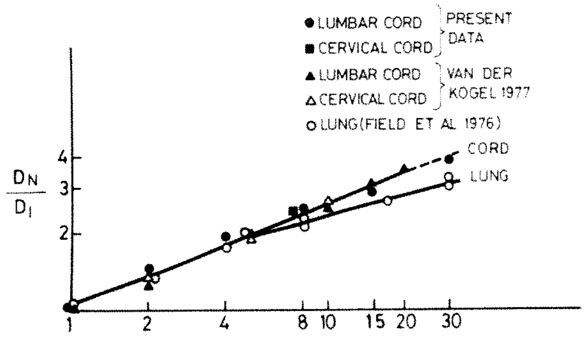


FIG. 6.

The relationship between dose and number of fractions for late damage to the cord is compared with late damage to the lung (Field, *et al.*, 1976). The ratio of total dose (D_N) over single dose (D_1) to produce the same effect is shown after the dose has been corrected for overall treatment time by $T^{\cdot 07}$ for lung.

Recent experiments on rat cervical cord by van der Kogel (1976) have produced a slightly different picture from that outlined here for lumbar cord. (D_2–D_1) at 24 hours was calculated to be 600 rad but no additional recovery occurred up to eight weeks after irradiation. However, at 16 weeks (D_2–D_1) had increased to 1000 rad and the exponent of the T factor was calculated to be 0.032. Van der Kogel suggests that this recovery between eight and 16 weeks may be due to repopulation by vascular endothelial cells. In the cervical cord the oligodendrocyte and vascular endothelial populations rather than the Schwann cells appear to be the most vulnerable to irradiation (van der Kogel and Barendsen, 1974). Sections of cervical cord from our irradiated animals show necrosis of the white matter: vascular damage is shown by the presence of haemorrhages. The different time course of recovery from irradiation damage in the lumbar and cervical cord could be due to the different sensitivities to irradiation and different turnover rates of cell types in the two regions as outlined above. However, we have found that the response of the cervical cord to eight fractions of X rays given over six weeks in our rats is similar to the response of the lumbar cord (Table II and Fig. 6). Van der Kogel (1977a) also found that the effect of fractionation was the same in both regions (see Fig. 6). Perhaps, therefore, the disparity between the results of van der Kogel and those presented here does not reflect differences between the lumbar and cervical region but some other factor, for example a difference in radiation response of the strains of rat used.

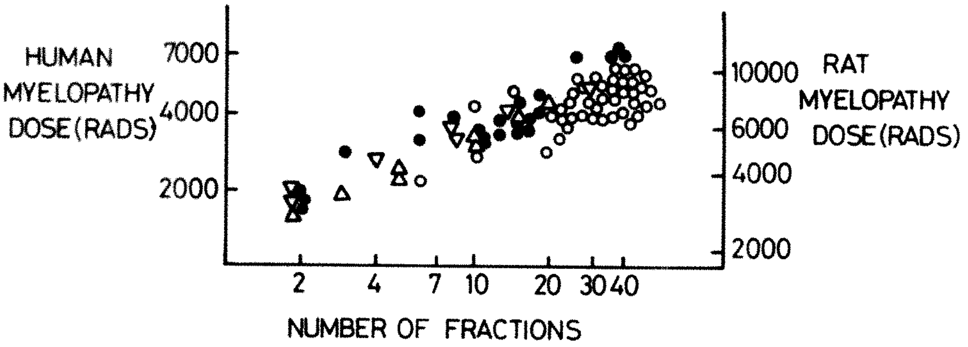


Fig. 7.

The incidence of myelopathy in patients receiving irradiation (1–4 MV X rays or Co^{60} γ rays) to the thoracic cord (Wara *et al.*, 1975) compared with the incidence in rats given doses to the cervical or lumbar cord (250 kV X rays).

● patients with myelopathy. ○ patients without myelopathy.
△ myelopathy in 50% of rats, Van der Kogel 1977,
▽ myelopathy in 50% of rats, present data.

Field *et al.* (1976) found that in lung the first rapid, phase of recovery following irradiation was followed by a much slower phase which continued up to 60 days after irradiation. The exponent of the *T* factor was found to be 0.07. To account for this they have suggested a process of slow repair of radiation damage similar to Elkind repair of sublethal damage but taking about 100 times as long. They have postulated that this slow repair process may be typical of slowly proliferating tissues such as kidney and liver. However, on the basis of the results presented here and also those of van der Kogel (1976), this type of slow repair does not occur in the rat spinal cord and such sparing as occurs with long overall treatment times could be explained by a wave of repopulation stimulated during the treatment period.

The effect of increasing the treatment time on the dose required to cause damage to the cord is so small as to have little bearing on the planning of radiotherapy schedules. Considerable sparing of the spinal cord is, however, likely to be achieved by using large numbers of fractions. It is interesting that although the type of damage caused by irradiation of the two regions of cord is different, the effects of dose fractionation are very similar. In both the lumbar and cervical cords the ED_{50} increases from 2400 rad for a single dose to just over 6000 rad for eight fractions in six weeks. This may indicate that the relationship between tolerance dose and fractionation established here for damage to the lumbar and cervical cord may be applied to all regions of the spinal cord. A correlation between the isoeffect relationship of radiation myelopathy in the rat spinal cord and that observed in patients is shown in Fig. 7. The data on patients are these published by Wara *et al.* (1975) on the thoracic cord and are compared with data on the cervical and lumbar cord of rats presented here. The rat data have been normalized to the human value at two fractions; the absolute doses for rat myelopathy would be about 1.8 times higher than the doses producing myelopathy in humans. A line drawn through the data from patients who received from two to 40 fractions and developed myelopathy has a similar slope to that for the animal data, *i.e.* 0.40. This shows that the animal data gives a good model for the human response and gives confidence in extrapolating from animal data to areas outside clinical experience. It also confirms the view, drawn from the measured response to fractionated treatment of the animal cord, that the best sparing of damage to the spinal cord can be obtained by extended fractionation of dose.

REFERENCES

Carsten, A., and Zeman, W., 1966. The control of variables in radio-pathological studies in mammalian nervous tissue. *International Journal of Radiation Biology, 10,* 65–74.

Cavanagh, J. B., 1968. Effects of X-irradiation in the proliferation of cells in peripheral nerve during Wallerian degeneration in the rat. *British Journal of Radiology, 41,* 275–281.

Ellis, F., 1969. Dose, time and fractionation: a clinical hypothesis. *Clinical Radiology, 20,* 1–8.

Field, S. B., Hornsey, Shirley, and Kutsutani, Y., 1976. Effects of fractionated irradiation on mouse lung and a phenomenon of slow repair. *British Journal of Radiology, 49,* 700–707.

Fowler, J. F., 1965. The estimation of total dose for different numbers of fractions in radiotherapy. *British Journal of Radiology, 38,* 365–368.

GERACI, J. P., THROWER, P. D., JACKSON, K. L., CHRISTENSEN, G. M., PARKER, R. G., and FOX, M. S., 1974. The relative biological effectiveness of fast neutrons for spinal cord injury. *Radiation Research*, *59*, 496–503.

GILMORE, S. A., 1972. Spinal nerve root degeneration in ageing laboratory rats: a light microscopic study. *Anatomical record*, *174*, 251–258.

INNES, J. R. M., and CARSTEN, A., 1961. Demyelinating or malacic myelopathy. *Archives of Neurology*, *4*, 190–199.

KOGEL, A. J. VAN DER, 1976. Radiation tolerance of the spinal cord: the dependence on fractionation and extended overall times. *IAEA Symposium on Radiobiological Research and Radiotherapy*, 1977, vol. I, 85–90.

1977a. Radiation tolerance of the spinal cord: time-dose relationships. *Radiology*, *122*, 505–509.

1977b. Radiation-induced nerve root degeneration and hypertrophic neuropathy in the lumbosacral spinal cord of rats: the relation with changes in ageing rats. *Acta Neuropathologica* (*Berl.*), *39*, 139–145.

KOGEL, A. J. VAN DER, and BARENDSEN, G. W., 1974. Late effects of spinal cord irradiation with 300 kV X rays and 15 MeV neutrons. *British Journal of Radiology*, *47*, 393–398.

MASTAGLIA, F. L., MCDONALD, W. I., WATSON, J. V., and YOGENDRAN, K., 1976. Effects of X-irradiation on the spinal cord: an experimental study of the morphological changes in central nerve fibres. *Brain*, *99*, 101–122.

MASUDA, K., REID, B. O., and WITHERS, H. R., 1977. Dose effect relationship for epilation and late effects on spinal cord in rats exposed to gamma rays. *Radiology*, *122*, 239–242.

WARA, W. M., PHILLIPS, T. L., SHELINE, H. E., and SCHWAYDER, J. G., 1975. Radiation tolerance of the spinal cord. *Cancer*, *35*, 1558–1562.

Book reviews

Bone marrow transplantation and other treatment after radiation injury. By H. Balner, (Martinus Nijhoff Medical Division—The Hague) pp. 83, 1977 (For The Commission of the European Communities), Dfl.27.50.

A generation ago there was much experimental activity to develop methods for chemical protection against the effects of ionizing radiation or to treat over-exposure if it occurred. Nuclear fission had newly become big business for peaceful and military purposes. Now we hear little about chemical protection: and laboratory or industrial accidents have been few (and military nuclear casualties fortunately nil). Thus most of us do not keep abreast of what is being done about the treatment of rare radiation casualties.

Originally the treatment of radiation casualties was also chemically orientated—the search for humoral or similar stimulators to recovery of cells of bone marrow. The successful treatment of lethally irradiated rodents in those early days was not due to magic biochemicals in administered bone marrow or spleen but to unpredicted successful transplantation. Some of the pioneer laboratories in these studies have pursued the investigations through dogs and monkeys to man. The objective has been not only the salvage of the rare radiation casualty but the development of bone marrow transplantation for the treatment of cases of aplastic anaemia, leukaemia and now "combined immunodeficiency diseases".

Dr. Hans Balner, the author of this 80-odd page monograph, has long been a member of one of these pioneer laboratories—TNO Rijswijk, Netherlands—and is Director of its Primate Center. He is thus perfectly equipped to review the subject. It could have been made a sensational story as for a Sunday newspaper, but rightly has been cast as a scientific review, complete with the dull bits and the still plenteous uncertainties. There are some 150 references, obviously not a complete bibliography, but a reasonable selection to give the studious reader a good start to any line he wishes to pursue. Inevitably, particularly in clinical transplantation for the diseases listed above, there have been later reports updating the information supplied to the end of 1976.

J. A. F. LOUTIT.

Nuclear medicine: clinical and technological bases. By J. T. Andrews, and M. Jean Milne, pp. 468, 1977 (John Wiley, Chichester; New York), £18·75.

This book is based on a three year course of lectures for technicians (or "nucleographers"), and aims to give a clear understanding of the principles of the subject as a basis for a good standard of practical procedure. After a good introductory chapter on the role of the technician in nuclear medicine, the first half of the book describes each system of the body and the relevant radioisotope procedures. This integrated approach is generally successful but occasionally confusing. The style is didactic and thorough, although rather pedantic at times. There are a number of points which one hopes will be tidied up in a subsequent edition. No mention is made of the hazards associated with iron hydroxide particles or of lung scanning in patients with diffuse pulmonary hypertension, a factor of some importance as it is envisaged elsewhere in the book that the technicians themselves may administer the radiopharmaceuticals. Few would agree with the optimistic view of the value of pancreas scanning and the quoted radiation dose to the liver from ^{75}Se selenomethionine (page 158) is incorrect. Certain sections are somewhat dated, *e.g.* the emphasis on ^{85}Sr in the chapter on bone, and although ^{67}Ga is mentioned several times in connection with tumour localization, there is no reference at all to its value in abcess localization.

The second half of the book contains detailed technical descriptions of the different tests and the physical principles underlying them. This section will be useful for reference and will serve as a model for the procedure sheets which should be available in any department to ensure a high and consistent standard of work.

This book fills a gap in the literature and will be a useful addition to any departmental library, particularly in those concerned with the training of technicians. It will not, in my view, have much appeal to clinical and scientific staff, as suggested in the foreword, but it will provide valuable and at times simulating reading for technicians and radiographers, not least if it occasionally provokes the question "why do we do that differently?".

E. P. WRAIGHT.

1978, *British Journal of Radiology*, *51*, 524–527

The response of *E. coli* AB2463 recA to fast neutron beams with mean energies in the range 4 to 27 MeV

By J. L. Redpath, Ph.D.*

Department of Radiation Oncology, Michael Reese Medical Center, Chicago, Illinois 60616, U.S.A.

(*Received July, 1977 and in revised form November, 1977*)

ABSTRACT

The radiosensitivity of *E. coli* AB2463 recA, given as the reciprocal of the mean lethal dose, D_0^{-1}, has been shown to be the same for four fast neutron beams with widely different energy spectra. It is proposed that this organism can be used to intercompare dosimetry on fast neutron beams with mean energies in the range 4 to 25 MeV with an accuracy of ±5%.

Dosimetry of photon beams in the 0.1 to 10.0 MeV range may be done with an accuracy approaching 1%. Techniques employed include both physical (*e.g.* ionization chambers, calorimetry) and chemical (Fricke dosimeter) methods (Attix and Roesch, 1968). Dosimetry of fast neutron beams is not yet as accurate (Bewley, 1970). There are several reasons for this lack of accuracy. They are related to uncertainty in the contamination of the neutron field by photons, uncertainties in the energy spectra of the incident neutrons and photons, and in the values for the quantities required to calculate the absorbed dose from ionization measurements. These quantities are W, the energy required per electron-ion pair in the gas filling the ionization chamber, $S_{\mathrm{gas}}{}^{\mathrm{TE}}$, the relative stopping powers of tissue-equivalent plastic to the filling gas, and $K_{\mathrm{TE}}{}^{\mathrm{muscle}}$, the ratio of neutron kerma for muscle tissue to tissue-equivalent plastic. Hence there is always interest in the development of new dosimetric techniques.

Biological dosimetry has not received the acceptance given to physical and chemical dosimetry, mainly because of variation of biological effectiveness (RBE) with LET and a seeming lack of accuracy compared to other techniques. However, in view of the shortcomings of physical dosimetry in fast neutron fields, a biological system with a well-defined response as a function of LET might prove useful as a radiation dosimeter. The bacterium *E. coli* AB2463 recA is such a system, its radiation sensitivity having been measured at LET∞ values of 0.4, 26 and 134 keV/μm (Munson *et al.*, 1967). Alper (1971) has reported that for this organism the RBE of Hammersmith neutrons (16 MeV d on Be) relative to 250 kV X rays is 1.06. This value can now be corrected to 0.98 in view of recent adjustments to the dosimetric calibration of the Hammersmith neutron beam (Parnell and Bewley, 1976). If this RBE of essentially unity were to be maintained for other fast neutron beams, this organism would be of value as a dosimeter for such beams.

The present paper presents data for the radiosensitivity of this organism measured on three fast neutron beams in the U.S.A. and one in the U.K., with mean neutron energies ranging from 4 to 25 MeV.

MATERIALS AND METHODS

Irradiation technique

At Fermilab, bacteria suspended in phosphate buffer (5×10^{-3} M, pH 7) were irradiated in Pyrex glass tubes (1.7 cm o.d., wall thickness 1 mm) held in a tissue-equivalent plastic jig which provided 21 mm of build-up, with the centre of the tube just downstream of the peak of the depth dose curve, and 9 mm of backscatter material. Some experiments were also performed with polyethylene plastic tubes and no significant change in survival curve parameters was seen. A dose rate of about 150 rad/min was obtained by exposing the samples inside the collimator housing at a distance of 50 cm from the thick Be target bombarded by 67 MeV protons. During irradiation the samples were bubbled with oxygen. Details of the facility and beam characteristics have been given by Cohen and Awschalom (1976).

Similar set-ups were used at the other institutions (University of Chicago, University of Washington and Hammersmith Hospital). Different jigs were used to position the centre of the tube at the peak of the respective depth dose curves.

Dosimetry

Neutron dose measurements at Fermilab were made in the jig at the irradiation position using an Exradin air-filled ionization chamber made with Shonka A-150 tissue-equivalent plastic walls. The output of the neutron flux monitors immediately downstream of the target was calibrated relative to these measurements. Additional monitors of relative neutron fluence took the form of aluminum discs mounted on the downstream side of the tissue-equivalent jig. The Al discs were analysed for ^{24}Na activity about 24 h after exposure.

---

*Present address: Department of Radiological Sciences, University of California, Irvine, California 92717, U.S.A.

Dosimetry was performed in essentially the same manner at the University of Chicago, University of Washington and Hammersmith Hospital. An identical ionization chamber to that used at Fermilab was employed at the University of Chicago.

Bacterial culture and plating

E. coli AB2463 recA was obtained from Dr. Barbara Bachman, Yale University. Bacteria were grown overnight at 37°C in Difco nutrient broth to a stationary phase concentration of 5×10^8/ml. Following irradiation the bacteria were suitably diluted in phosphate buffer (5×10^{-3} M, pH 7) and plated on Difco nutrient agar.

RESULTS AND DISCUSSION

Survival curve parameters

Survival was measured of eight doses at 1 krad intervals for the neutron beam studies (see Fig. 1) and at 12 doses at 1 krad intervals for the low LET sources. Table I gives values of n (extrapolation number) and D_0 (mean lethal dose) for *E. coli* AB2463 recA measured on four fast neutron beams of widely different mean energy, and on several low LET sources. The parameters were obtained by linear regression analysis of the survival data. Also included is a published value obtained with the fission neutrons from the Janus Reactor at Argonne National Laboratory.

Since the Hammersmith group quotes dose in terms of neutron dose only, whereas the groups in

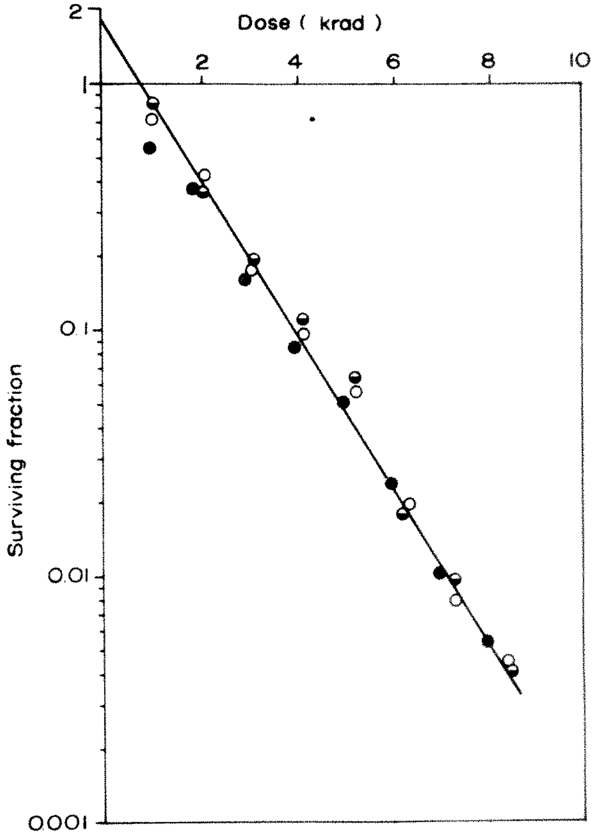


FIG. 1.

Survival curve for *E. coli* AB2463 recA suspended in buffer and irradiated with the Fermilab neutron beam (67 MeV p on Be). The three different sets of data points represent three separate experiments. The line is a best fit to the exponential portion of the survival curve as determined by linear regression analysis.

TABLE I

SURVIVAL CURVE PARAMETERS FOR *E. Coli* AB2463 RECA IRRADIATED WITH BEAMS OF DIFFERENT QUALITY

Radiation source	Mean energy (MeV)	n*	D_0† (Krads)
Hammersmith 250 kV X ray[1]		1	1.33
MRH ^{60}Co		1.92±0.30	1.24±0.10
MRH 6 MeV photons		1.68±0.20	1.29±0.04
MRH 25 MeV electrons		1.97±0.50	1.35±0.10
Hammersmith neutrons (16 MeV d on Be)	7.5	1.03±0.02	1.41±0.10
University of Chicago neutrons (8.3 MeV d on Be)	4.0	0.99±0.10	1.34±0.04
University of Washington neutrons (21 MeV d on Be)	8.0	1.03±0.03	1.38±0.02
Fermilab neutrons (67 MeV p on Be)	25.0	1·75±0.01	1.39±0.04
Janus Reactor, Argonne[2]	0.8	1	3.97

*n = extrapolation number
†D_0 = mean lethal dose
Errors are ±1 standard deviation
Surviving fraction $f = {}_{\mathrm{ne}} - D/D_0$
MRH = Michael Reese Hospital
[1] Alper (1971).
[2] Peak and Ainsworth (1973).

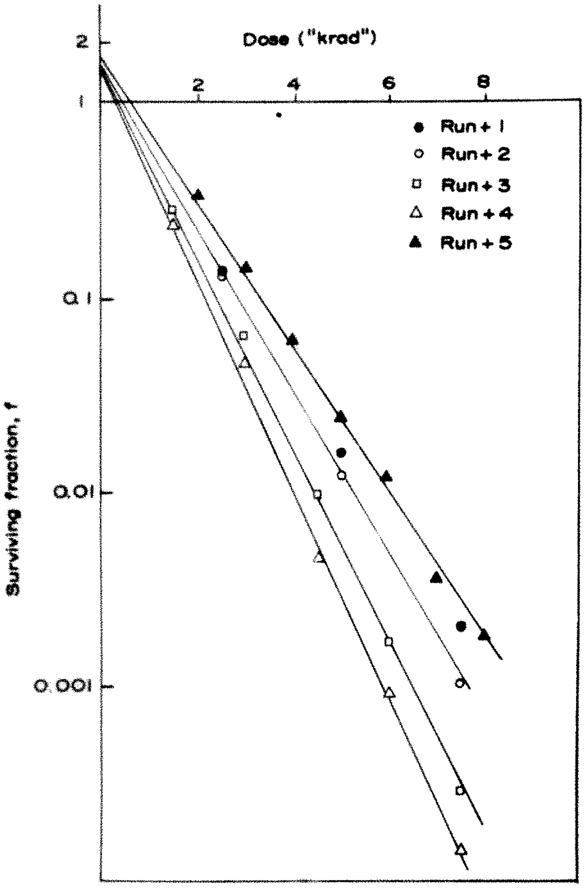


Fig. 2.

Survival curves for *E. coli* AB2463 recA suspended in buffer and irradiated on five separate occasions during development of the Fermilab neutron beam (67 MeV p on Be).

the USA quote total dose ($n+\gamma$), the Hammersmith D_0 in Table I is a corrected value to account for the 10% γ-ray contribution under the conditions of that experiment (Bewley, private communication). The data in Table I show the D_0 to be the same within experimental error (±5%) for the different fast neutron beams even though their mean energy varied from 4 to 25 MeV. Any variations in D_0 with mean neutron energy may well be masked by systematic errors in physical dosimetry and experimental error. Assuming the physical dosimetry of the neutron beams used is accurate to within ±5%, the RBE (in terms of D_0 ratios) relative to several low LET sources is 0.95 ± 0.05. Thus the response of *E. coli* AB2463 recA can be used to intercompare dosimetry on fast neutron beams with mean energies in the range studied to an accuracy of ±5%.

In initial dosimetric and radiobiological studies with the fast neutron beam (67 MeV p on Be) at Fermilab during development of the beam it was decided to employ *E. coli* AB2463 recA as a dosimeter in addition to an air-filled, tissue-equivalent ionization chamber. Aluminum discs were used as neutron fluence monitors. Survival curves obtained on five such occasions are shown in Fig. 2. Clearly there were variations in the nominal dose on these different days and these were also reflected by the measurements of Al activity (Fig. 3). Day-to-day variations in physical dose measurements were later traced to faulty software in the computerized monitoring system. When survival was plotted against Al activity the points fitted well to a straight line (Fig. 4). Later experiments conducted at Fermilab (*e.g.* Fig. 1) indicated the RBE for Fermilab neutrons to be 0.95. It was then possible to calibrate the ^{24}Na activity of the Al discs to give the dose in rad.

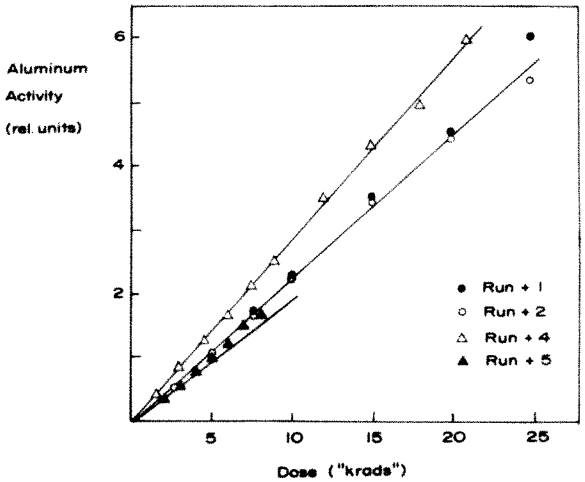


Fig. 3.

Measurements of aluminum activity as a function of nominal dose for Al discs irradiated in conjunction with *E. coli* AB2463 recA on four separate occasions with the Fermilab neutron beam (67 MeV p on Be).

Biophysical considerations

From studies of bacterial radiosensitivity as a function of LET it has been established that for LET$_\infty$ greater than 20 keV/μm the phenomenon of "overkill" occurs and radiosensitivity decreases (Munson *et al.*, 1967; Alper *et al.*, 1967). For the fast neutron beams considered in this study a considerable fraction (30–50%) of the absorbed dose is at LET values greater than 20 keV/μm (Bewley, 1968; Amols *et al.*, 1978; Weaver, private communication). In order that the RBE should be close to unity for these beams this organism must show a peak in radiosensitivity with LET at around 20 keV/μm. This is contrary to the indications of the limited

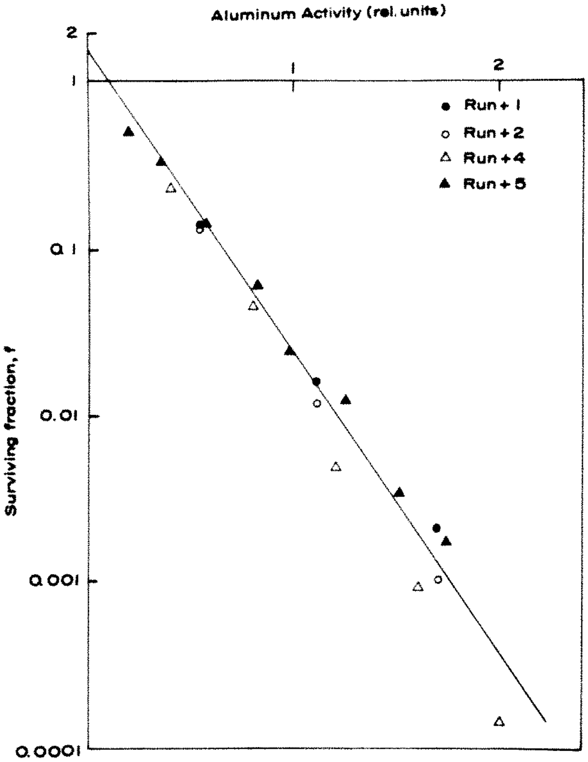


FIG. 4.

Surviving fraction plotted against Al activity measurements (combining data of Figs. 2 and 3).

data for *E. coli* AB2463 recA published by Munson *et al.* (1967) which indicate a flat response followed by overkill. Clearly it would be desirable to conduct a carefully controlled study of the response of this organism as a function of LET∞.

Included in Table I is a value of D_0 measured with the fission neutron beam from the Janus Reactor by Peak and Ainsworth (1973). This D_0 is considerably greater than that measured on the higher energy fast neutron beams indicating a large amount of "overkill" in bacteria with fission neutrons. This is consistent with calculations which estimate that about 90% of the absorbed dose is at LET values greater than 20 keV/μm for fission neutrons (Bewley, 1968).

ACKNOWLEDGMENTS

The encouragement and advice of Drs. L. Cohen, M. Awschalom, D. Young, and Mr. A. Jones (all of Cancer Therapy Facility, Fermilab), Dr. F. Kuchnir (University of Chicago), Dr. J. Ovadia (Michael Reese Hospital), and Dr. T. Alper (Gray Laboratory) is gratefully acknowledged. The physicists and biologists at the various neutron facilities are thanked for their co-operation. Partial support for this work came from Public Health Service Grant No. 1 PO 1 CA 18081-01.

REFERENCES

ALPER, T., 1971. In *Biophysical aspects of radiation quality*, IAEA-SM-145-1, pp. 171–183 (Vienna).

AMOLS, H. I., DICELLO, J. F., AWSCHALOM, M., COULSON, L., JOHNSEN, S. W., and THEUS, R. B., 1978. Physical characterization of neutron beams produced by photons and deuterons of various energies bombarding beryllium and lithium targets of several thicknesses. *Medical Physics 4*, 486–493.

ATTIX, F., and ROESCH, W. C. (eds.), 1968. *Fundamentals of Radiation Dosimetry*, Vols. I, II, III (Academic Press, N.Y./London).

BEWLEY, D. K., 1968. Calculated LET distributions of fast neutrons. *Radiation Research*, *34*, 437–445.

1970. Fast neutron beams for therapy. *Current Topics in Radiation Research*, *6*, 249–292.

COHEN, L., and AWSCHALOM, M., 1976. The cancer therapy facility at the Fermi National Accelerator Laboratory, Batavia, Illinois: a preliminary report. *Applied Radiology*, Nov.–Dec., 51–60.

MUNSON, R. J., NEARY, C. J., BRIDGES, B. A., and PRESTON, R. J., 1967. The sensitivity of *Escherichia coli* to ionizing particles of different LET's. *International Journal of Radiation Biology*, *13*, 205–224.

PARNELL, C. J., and BEWLEY, D. K., 1976. Dosimetry of the fast neutron beam produced by the MRC cyclotron. *British Journal of Radiology*, *49*, 298.

PEAK, M. J., and AINSWORTH, E. J., 1973. Inactivation of ultra-violet sensitive mutants of *Escherichia Coli* by fast neutrons. Argonne National Laboratory Ann. Report (ANL-8070), pp. 195–196.

Book review

Erkrankungen des Magens (*Diseases of the Stomach*). Contributions by M. Classen, W. Dolle, W. Frik, R. Herzer, W. Holthusen, G. Kieninger, B. Kommerell, L. Koslowski, D. Meyer, D. Schoen, K.-Fr. Sewing, H. J. Sielaff, and R. Siewert, pp. 142., illus, 1977 (Georg Thieme Verlag, Stuttgart), DM.54.

This is a multidisciplinary review of the diseases of the stomach written with the radiologist in mind, to keep him up to date with the examination of the stomach in adults and infants, using radiological endoscopic and radioisotope techniques. There are chapters on the physiology and pathological anatomy of the stomach, on the medical and surgical treatment of gastric lesions and on post-operative appearances. The book brings together much old and new information from a fast expanding field of knowledge. It will be of great value to the practising radiologist. There are good lists of references. A very useful book.

G. M. STEINER.

1978, *British Journal of Radiology*, *51*, 528–529

Technical notes

Colonic lavage prior to barium enema—a comparison of two techniques

By E. Bresnihan, D.Ch., D.Obst., R.C.O.G., F.R.C.R.,[*] F. T. de Dombal, F.R.C.S.,[†]
G. J. S. Parkin, B.Sc., F.R.C.R., S. E. W. Smith, F.R.C.R., S. Fakes, S.R.N., and J. Horrocks[†]

Departments of Diagnostic Radiology[*] and University Department of Surgery[†], St. James University Hospital, Leeds

(*Received March, 1977 and in revised form December, 1977*)

A clean colon is a prerequisite to a successful double contrast barium enema. Two different techniques of colonic lavage have been in use in this hospital for some years, one employing the Henderson colonic lavage machine (MacCarthy's Surgical Division) and the other, a simpler method, which we deem "the shortened preparation". As the latter technique is more acceptable to the patient, simpler to perform and requires no specialized equipment, we thought a comparison of the results of both techniques would be of interest.

METHODS

The films of the double contrast enemas of 40 outpatients were examined retrospectively. All had been examined using the St. Mark's modification of the Malmö double contrast barium enema (Young, 1964), but taking only double contrast films on six of which the rectum is included. The examinations were selected by one of us (S.F.). Twenty patients from each group, matched for sex and age, were chosen.

Preparation before attending the department was similar in both groups, namely three Senokot (SDX) tablets at 21.00 hours two nights before and 1 oz. (28.35 g) of castor oil at 14.00 hours on the day prior to the examination. Apart from an early morning drink, no food was allowed on the day of attendance. 1 mg of Atropine was given orally, unless medically contra-indicated, when the patient arrived in the department.

Each patient in the Henderson machine group had two pints of warm water containing 3 g of Veripaque instilled into the colon by a Higginson syringe. This was followed by 20 minutes sitting on the toilet. Colonic irrigation with the Henderson machine was then carried out until the returning fluid was clean. An average of 40 pints of water was used (range 26–80).

The "shortened preparation" group had 2–3 pints (1.136–1.704 l) of warm water instilled rectally using a Higginson syringe. After 20 minutes on the toilet this was repeated with the addition of 3 g of Veripaque. Again the patient was sent to the toilet for a minimum of 20 minutes. A delay of one hour was considered mandatory before the barium enema.

The 40 double contrast barium enemas were assessed blindly and independently by three radiologists. Three parameters were assessed, namely, mucosal coating, retained fluid and residual faeces. Each category was scored from one to five.

RESULTS

Overall scores (Table I)

The difference in scoring (596 vs 566) is not statistically significant ($X^2 > 1, p < 0.2$).

TABLE I

COMPARISON OF TOTAL POINTS GIVEN FOR EACH ASPECT OF TECHNIQUE IN BOTH GROUPS

	Total Group Score	
	"Shortened preparation"	Henderson
Residual faeces	196	200
Mucosal coating	203	181
Retained fluid	197	185
Total score	596	566

Differences are not statistically significant.

TABLE II

ASSESSMENT OF RESIDUAL FAECES IN EACH GROUP, SCORES OF ALL THREE ASSESSORS

	'Shortened preparation"	Henderson
Excellent/good	25	28
Moderate	24	18
Poor/very poor	11	14
Total	60	60

Differences in distribution are not statistically significant.

1978, *British Journal of Radiology*, *51*, 529–531 JULY 1978

TABLE III

COMPARISON OF 60 ASSESSMENTS OF MUCOSAL COATING IN EACH OF THE TWO GROUPS

	"Shortened preparation"	Henderson
Excellent/good	29	13
Moderate	25	3
Poor/very poor	6	14
Total	60	60

Differences are statistically significant: $X^2 = 8.805$, $df = 2$, $p < 0.02$

TABLE IV

COMPARISON OF RETAINED FLUID (60 ASSESSMENTS) IN EACH OF TWO GROUPS

	"Shortened preparation"	Henderson
Excellent/good	25	18
Moderate	26	28
Poor/very poor	9	14
Total	60	60

Differences are not statistically significant.

Residual Faeces (Table II)

The difference in distribution is not statistically significant ($X^2 \simeq 0.5$, $df = 2$, $p > 0.2$).

Mucosal coating (Table III)

The "shortened preparation" group scored better than the Henderson technique. The differences are statistically significant ($X^2 = 8.805$, $df = 2$, $p < 0.02$).

Retained Fluid (Table IV)

There is a marginal advantage in favour of the "shortened preparation". However, the difference is not statistically significant.

DISCUSSION

The time taken to perform the two different methods of colonic lavage was similar. Patients tolerate better the "shortened preparation". Those patients who had had a previous barium enema performed and were able to compare the two techniques, expressed a preference for the "shortened preparation". The two main complaints of the Henderson lavage group were the discomfort of the two-way rectal nozzle, particularly where local anal lesions such as haemorrhoids were present, and the difficulty of lying in the lateral position throughout the lavage. These complaints were age related, being more marked in the elderly. Whilst both methods are undoubtedly adequate preparation for a successful double contrast barium enema, we can adduce no evidence from the statistical data that the Henderson technique is superior to the "shortened preparation" Indeed in one respect, mucosal coating, it is significantly worse.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. E. A. Power and Mrs. M. Fierheller for secretarial help and also the radiographic and nursing staff of St. James's University Hospital for their help in producing this paper.

REFERENCE

YOUNG, A. C., 1964. The Malmö enema at St. Mark's Hospital: a preliminary report. *Proceedings of the Royal College of Medicine*, *57*, 275–278.

Reciprocity law failure with film/screen combinations for mammography

By W. W. Seelentag, Dipl.-Phys., Ph.D., and W. Panzer, Dipl.-Phys.

Gesellschaft für Strahlen- und Umweltforschung mbH München D-8042 Neuherberg, West Germany

(*Received November, 1977 and in revised form February, 1978*)

In radiology the validity of the reciprocity law is usually assumed: the film density for a given X-ray spectrum depends only on the tube exposure (the mAs), and not on the exposure time. This reciprocity law holds for non-screen films (Morgan, 1944). For screen/film combinations, where most of the film density is due to exposure to light from the screen, reciprocity law failure may occur. However, for materials used nowadays in general radiology the effect is negligible for exposure times from 0.005 to 1 second. During the course of measurements on film/screen combinations used in mammography, exposure times of up to 20 minutes had to be used (Panzer, *et al.*, 1978). Therefore reciprocity law failure of these materials had to be investigated. It was found that even at an exposure time of 5 seconds the system speed is reduced by some 30% due to reciprocity law failure.

Theory of Reciprocity Law Failure

Reciprocity law failure is described in many textbooks, *e.g.* by Mees and James (1962) and Herz (1969). Photographic emulsions are most sensitive when the intensity of the exposing radiation is such that an exposure time between 0.01 and 10 seconds is required to produce a medium film density. Decreased sensitivity may occur at higher or lower intensities. For technical reasons only the low-intensity reciprocity law failure needs to be considered for medical radiography. Indirectly it is accounted for by distinguishing between time-scale and intensity-scale sensitometry. Some understanding of the processes occurring during the blackening of a silver halide film is necessary. According to the model described by Gurney and Mott (1938), so-called sensitivity specks, *i.e.* silver sulphide impurities of the AgBr grain, are essential for latent image formation. A photon absorbed in the grain produces photoelectrons, which in turn produce slow electrons. These electrons can move freely in the conduction band until they are trapped in a sensitivity speck. The sensitivity speck becomes negatively charged and attracts positive silver ions from interstitial sites. The (neutral) silver speck initiates the reduction of the AgBr grain to metallic silver during development, but is not stable below a certain size. With direct X-ray exposure a large enough silver speck is produced by a single photon. With visible-light exposure, on the other hand, a number of photons need to be absorbed. If the time between two subsequent absorptions is too long

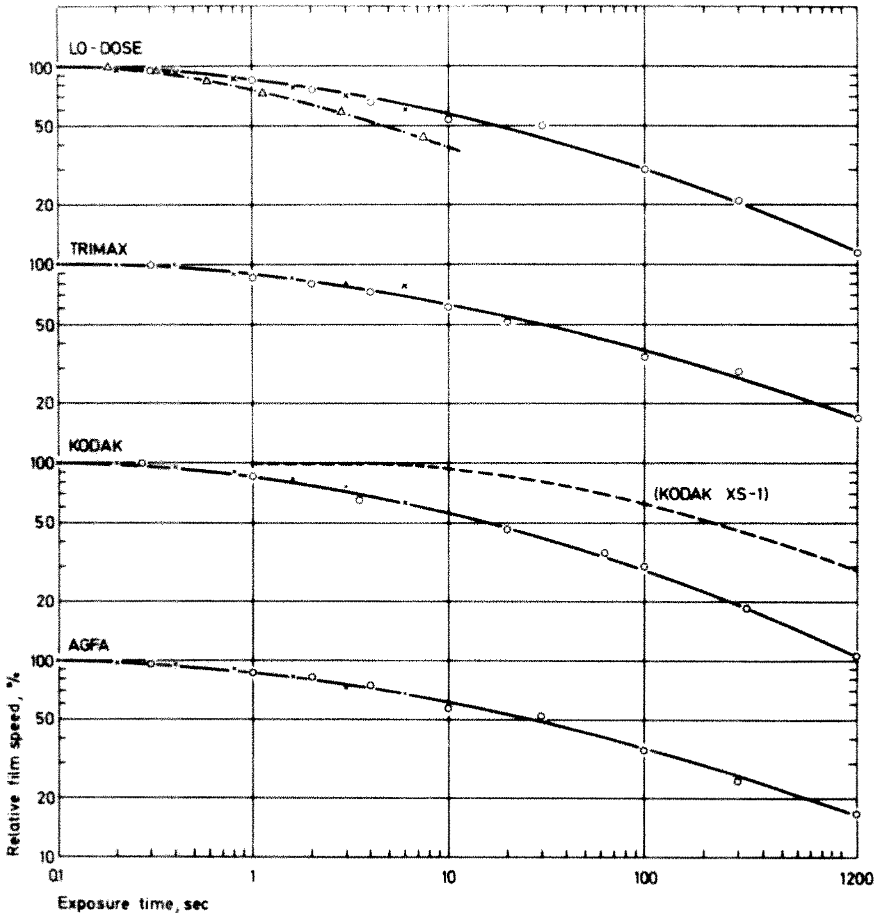


Fig. 1.

Relative speeds of four film/screen combinations used in mammography versus exposure time. Measurements were carried out using X rays (crosses) and visible light (circles). Also included are measurements on a double-coated film used in general radiology (dashed line), and a curve (triangles) based on data published by Friedrich and Weskamp (1976) and shown in the uppermost section.

thermal dissociation of the small silver speck may occur. This results in a decreased sensitivity at low intensities.

MEASUREMENTS

Two types of measurement were carried out:

(a) exposure of the film/screen combination to X rays, and

(b) exposure of the film to visible light.

Measurements with X rays were carried out with exposure times between 0.1 and 6 seconds. As some 5 to 8% of the film blackening is due to direct interaction of the film emulsion with the X rays, this measurement is not exactly a measurement of reciprocity law failure, but rather of the effect of reciprocity law failure on the system speed. With increasing exposure time the percentage of direct film blackening increases as the sensitivity of this process is not reduced by reciprocity law failure. For this reason the measurements at long exposure times were carried out by light exposure. As both sets of measurements agree at short exposure times within the (estimated) error of about ±10% they are reproduced together in Fig. 1.

X-ray exposures

The film/screen combinations were exposed to 90 kV X rays at 40 mA. The intensity was adjusted by different filtrations (depending on the system speed, and constant for a given system). H & D curves were determined by varying the FFD from 50 to 560 cm. Each exposure was measured with an ionization chamber (35 cm^3, EIL). After machine processing (Kodak X-Omat) the densities were measured with a calibrated McBeth densitometer. The exposures necessary for a net density of 1 were read off the resulting H & D curves for all exposure times. The relative speeds were calculated relative to 100% at the shortest exposure time (0.1 second). The exact shape of the X-ray spectrum does not influence the results presented in Fig. 1, which are only relative values for a given film/screen combination.

Visible-light exposures

A photographic enlarger with added filter (Kodak, Wratten 39) was used as a light source. As relative measurements of reciprocity law failure are almost independent of wavelength (Mees and James, 1962) a better simulation of the fluorescent light emitted by the intensifying screen was not necessary. The light intensity was varied using grainless neutral density filters (Agfa "N060" and "N200"). The manufacturer's filter specifications were checked using the calibrated densitometer. For a given exposure time the H & D curve was determined by varying the aperture, aperture settings having been calibrated using a luxmeter. The constancy of the light output was checked before and after each set of measurements with the luxmeter. The relative speeds were calculated as with the X-ray exposures.

RESULTS AND CONCLUSIONS

The results for four common film/screen combinations are reproduced in Fig. 1. Included for comparison are measurements on a double-coated film used for general radiology, and a second curve for one of the mammography systems. This second curve is based on the difference between H & D curves at constant exposure time and constant exposure rate, published by Friedrich and Weskamp (1976). As the data were read off their graphs the error associated with this curve will be large.

Although the exposure times used in our experiments are much longer than exposure times used during routine mammography, the results shown in Fig. 1 indicate that reciprocity law failure might not be negligible at exposure times of a few seconds common in clinical routine.

Since acceptance of this technical note an article on "Measurements of reciprocity law failure in green-sensitive X-ray films" giving comparable results for double coated films, has been published (Arnaold *et al.*, 1978).

REFERENCES

Arnaold, B. A., Eisenberg, H., and Bjärngard, B. E., 1978. Measurements of reciprocity law failure in green-sensitive X-ray films. *Radiology*, *126*, 493–498.

Friedrich, M., and Weskamp, P., 1976. Bildgütefaktoren bei der Filmmammographie. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *125*, 269–278.

Gurney, R. W., and Mott, N. F., 1938. The theory of the photolysis of silver bromide and the photographic latent image. *Proceedings of the Royal Society* (*London*) *Ser. A.*, *164A*, 151 (cited in Herz, 1969).

Herz, R. H., 1969. *The Photographic action of ionizing radiations* (Wiley-Interscience, New York).

Mees, C. E. K., and James, T. H., 1962. *The theory of the photographic process* (MacMillan, New York).

Morgan, R. H., 1944. Reciprocity law failure in X-ray films. *Radiology*, *42*, 471–479.

Panzer, W., Drexler, G., Platz, L., and Widenmann, L., 1978. Spektren und Dosiswerte in der Mammographie. *GSF-Report*, *S–518* (in press).

1978, *British Journal of Radiology*, *51*, 532–534

Technical notes

Good thermal dosimetry is essential to good hyperthermia research

By J. E. Robinson, Ph.D., G. H. Harrison, Ph.D., W. A. McCready, B.S., and
G. M. Samaras, E.E., Ph.D.

Division of Radiation Therapy, University of Maryland School of Medicine, Baltimore, Maryland 21201, U.S.A.

(*Received December, 1977*)

Our group has carried out a series of hyperthermia studies using third generation transplants of spontaneous mammary tumours on the flanks of C3H mice. The tumours were heated by immersion in water baths and considerable effort has been expended to characterize the thermal uniformity of the tumour under treatment conditions (Robinson *et al.*, 1975). The results indicated that the tumours were uniform in temperature to about 0.1°C and were within about 0.1°C of the temperature of the water bath.

Data taken with this tumour heated by means of a water bath showed a dramatic effect of hyperthermal treatment on tumour radiosensitivity (Robinson *et al.*, 1972). In addition, a comparison of these tumour data with comparable data from normal mouse skin showed that a therapeutic advantage might be gained by radiation treatment at elevated temperatures (Robinson *et al.*, 1974). Data from other laboratories, primarily from tumours implanted on the legs of mice and also heated by immersion in water baths (Thrall *et al.*, 1975), show smaller therapeutic advantages for similar water bath temperatures.

To broaden our heating capability we have developed microwave heating techniques applicable to small laboratory animals (Robinson, *et al.*, 1976; 1977). One of our approaches has been to immerse the tumour in liquid bolus in plane-parallel-slab geometry and to irradiate with parallel opposed microwave beams—a direct analogy with radiation therapy techniques used with X radiation. The liquid bolus is a mixture of water, ethanol and sodium chloride; it is tissue equivalent for the microwave frequency used in this study (2.45 GHz). We have been evaluating the thermal uniformity of the same tumours implanted subcutaneously on the legs of mice and immersed in liquid bolus at elevated temperatures prior to microwave heating. In contrast to the good thermal uniformity of the tumours on the flank, the tumours on the leg have been found to be quite non-uniform in temperature.

Temperature distributions were measured by drawing small thermistor probes through the tumour, along parallel lines at different distances

---

This work was supported in part by National Cancer Institute Grant No. CA18872–01 and American Cancer Society Grant PDT 33.

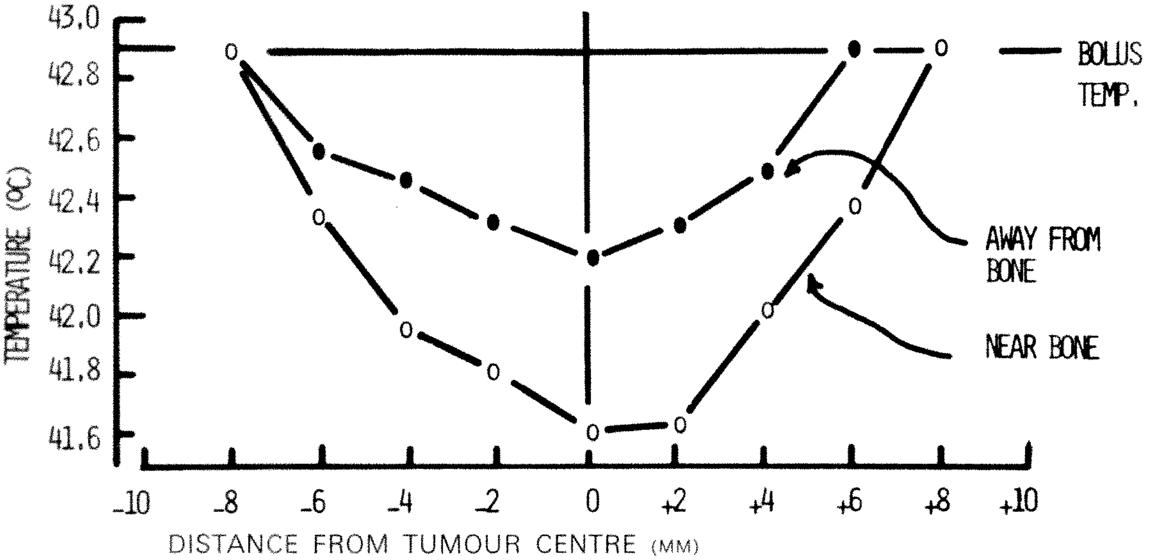


FIG. 1.

Thermal profiles of mouse mammary tumours implanted in the leg and immersed in liquid bolus at 42.9°C

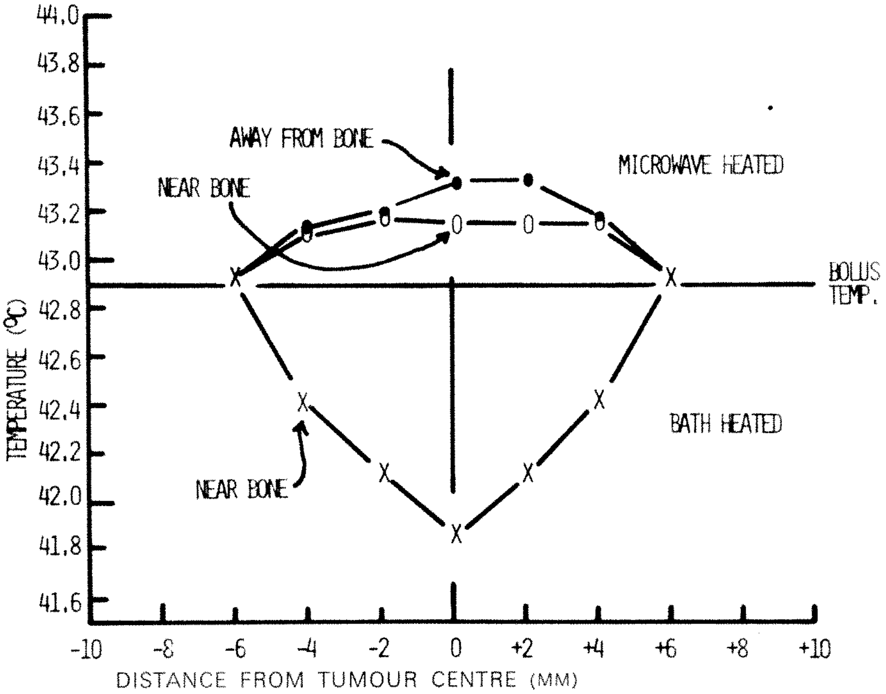


Fig. 2.

Thermal profiles of mouse mammary tumours implanted in the leg and immersed in liquid bolus at 42.9°C with additional microwave heating.

from the bone and leg muscle. Two such thermal profiles are shown in Fig. 1, one of which was taken along a line near the leg bone but well within the tumour. The second was taken about one-third of the way into the tumour on the side away from the bone. The tumour was roughly ellipsoidal in shape and measured 15×12×8.5 mm along the three orthogonal major axes. The water bath in which it was immersed was maintained at 42.9°C. Both profiles show marked temperature variations with the temperatures falling to 41.6 and 42.2°C for the thermal scans near and away from the bone.

Figure 2 gives another example of the cold central region near the bone of a smaller tumour (10×8×5 mm) also heated by immersion, together with the more uniform thermal pattern of tumours immersed in liquid bolus and heated with microwaves. The liquid bolus was maintained at 42.9°C and the bolused tumour was irradiated with a microwave power of 22 watt. Heating with combined microwaves and temperature-controlled liquid bolus much improved the thermal uniformity as is shown in the top two curves.

Non-uniformity in temperature of the tumours heated by water bath alone can be attributed to two factors: major vessels run down both ventral and dorsal aspects of the leg and act as heat pipes to cool the tumour locally. In addition, in order to reach the inner aspect of the tumour, heat must be transferred through the muscle and bone of the leg. The cooling effect of blood flow near the bone is also evident in the lower temperature achieved near the bone when the tumour was heated with microwaves.

Because of the strong dependence of thermal and radiation sensitivities on temperature, the cold spots which we see in these tumours would markedly affect any measure of tumour response. In assays such as tumour cure and time of tumour regrowth, the measured response is probably characteristic of the lowest temperature experienced by any significant fraction of the tumour under treatment. Thus tumours in the leg immersed in water baths at 45.0°C might more appropriately be compared with uniformly heated tumours immersed in water baths 1–1.5°C lower in temperature.

These observations might have some bearing on the discrepancies in biological hyperthermia data on different tumours subjected to apparently similar thermal treatments. They should stand as a reminder that careful thermal studies are even more important to thermobiology than good radiation dosimetry is to conventional radiobiology.

1978, *British Journal of Radiology*, *51*, 534–538

REFERENCES

ROBINSON, J. E., WIZENBERG, M. J., EDELSACK, E. A., and MCCREADY, W. A., 1972. Thermally enhanced radiocurability of mammary tumours in C3H mice. (Abstract) International Union for Pure and Applied Biophysics. Academy of Sciences of the USSR.

ROBINSON, J. E., WIZENBERG, M. J., and MCCREADY, W. A., 1974. Hyperthermia and radiation-response of normal tissue *in situ*. *Radiology*, *113*, 195–198.

ROBINSON, J. E., MCCULLOCH, D., and EDELSACK, E. A., 1975. Evaluation of tumour immersion technique for radiobiological hyperthermia studies. (Abstract). *Medical Physics*, *2*, 159.

ROBINSON, J. E., MCCULLOCH, D., and EDELSACK, E. A., 1976. Microwave heating of malignant mouse tumours and tissue equivalent phantom systems. *Journal of Microwave Power*, *11*, 87–98.

ROBINSON, J. E., MCCULLOCH, D., CHEUNG, A., SAMARAS, G., and SLAWSON, R. G., 1977. Microwave bolusing: a technique for improving heating uniformity for microwave hyperthermia. (Abstract) *Medical Physics*, *4*, 336.

THRALL, D. E., GILLETTE, E. L., and DEWEY, W. C., 1975. Effect of heat and ionizing radiation on normal and neoplastic tissues of the C3H mouse. *Radiation Research*, *63*, 363–377.

A linear transform of the multi-target survival curve

By J. V. Watson, M.A., M.Sc., F.R.C.R

University and MRC departments of Clinical Oncology and Radiotherapeutics, The Medical School, Hills Road, Cambridge, CB2 2QH

(Received November, 1977 and in revised form February, 1978)

Survival curves of mammalian cells following low LET irradiation are characterized by an initial shoulder region which tends to an exponential decline at higher doses. The experimental data are most easily analysed by assuming the multi-target model, excluding the data points on the shoulder and carrying out a log-linear regression analysis to give the slope, $1/D_0$, and the extrapolation number, N, (Alper, *et al.*, 1960). Apart from the assumption of the model, this analysis has the disadvantage that a subjective assessment must be made about where the shoulder ends, and hence which data points to exclude.

The method of analysis presented here was developed to overcome this disadvantage by transforming the multi-target curve to linear form which allows all the data to be included in the analysis. The method was tested with data obtained from the EMT6 tumour for hypoxic and oxic cells, and the results have been compared with those from conventional methods of analysis.

THEORY

The multi-target survival curve,

$$S = 1 - (1 - \exp(-D/D_0))^N \qquad . \qquad . \quad (1)$$

may be transformed to linearity as follows. From (1) we may obtain,

$$\ln(1 - S) = N \ln(1 - \exp(-D/D_0)) \quad . \quad (2)$$

Dividing through by N, and exponentiating both sides we get,

$$\exp\left(\frac{\ln(1-S)}{N}\right) = 1 - \exp(-D/D_0)$$

Therefore $1 - \exp\left(\frac{\ln(1-S)}{N}\right) = \exp(-D/D_0)$

Taking logs we get,

$$\ln\left(1 - \exp\left(\frac{\ln(1-S)}{N}\right)\right) = -D/D_0 \quad . \quad (3)$$

There are two unknown quantities, N and D_0, in this equation which is of the form $Y = mX + C$. The left-hand side of equation 3 is equivalent to Y and the transformed data are dependent on the value of N. The slope, m, is given by $-1/D_0$ and the intercept, C, will be zero for a unique value of N.

A program written to carry out the analysis proceeds as follows:

1. The data are transformed with an initial guess for the value of N. In practice it has been found that most data can be analysed rapidly by setting N with a provisional value of five.
2. A linear regression analysis is carried out which gives values for the slope and intercept. The latter should be zero and a t-test is carried out to test for this condition. If there is a probability of greater than 0.995 that the regression line for the transformed data passes through the origin then the values of N and D_0 are output as the parameters for the multi-target survival curve which "best fits" the experimental data.
3. If, for the initial guess for the extrapolation number, N, the condition specified in 2 above is not met, a better approximation, N_1, can be found from the non-zero value of C. From equation (2) it can be shown that

$N_1 \ln(1 - \exp(\bar{x}\, m)) = N \ln(1 - \exp((\bar{x}\, m) + C))$ where $\bar{x}$ is the mean of all the x values, m is the initial approximation for the slope and N is the approximation for the extrapolation number which gives rise to the non-zero value of C.

4. This second approximation for N is now employed to re-transform the survival data and the program returns to step two.

5. Once the value for N has been found which causes the regression of the transformed data to pass through the origin, the program prints out this value of N, the slope, D_0, confidence limits and transformed data.

6. The constraint placed upon the linear transform analysis which forces the regression to pass through the origin does not necessarily result in a minimum residual sum of squares. The value of N is now varied until the minimum residual is found. The "unexplained" variance due to residuals obtained with the constraint of intersecting the origin is now compared with that from the calculation for minimum residuals, "unconstrained" computation, by means of the F ratio.

7. A further modification has also been written which will analyse two sets of data, *e.g.* for oxic and hypoxic states. This employs the principles of the Pike-Alper method (1964) using a common value of N for the data. The first stage of this subsidiary routine analyses both sets of data as already described. If a common value for N can be found it will lie between the values found in the independent first stage analyses. An iterative procedure is employed to find the common value of N which will give rise to equal probabilities that the regressions of both sets of transformed data will pass through the origin. The criteria for accepting the results from the four parameter hypothesis (independent values of N) or the three parameter hypothesis (common value of N) are those described by Pike and Alper (1964).

RESULTS

The analysis is illustrated with radiation survival data from the EMT6 tumour growing *in vivo* (Bleehen *et al.*, unpublished data). Hypoxic cells were obtained from anaesthetised tumour-bearing mice asphyxiated with nitrogen ten minutes before irradiation. The EMT6 tumour growing *in vivo* contains a fraction of about 30% hypoxic cells (Rockwell and Kallman, 1973; Bleehen *et al.* unpublished data). To obtain survival data for oxic cells the tumours were excised, single cell suspensions were prepared and these were irradiated *in vitro* before plating out. Irradiations were carried out with 250 kV X rays with a half-value layer of either 2.4 mm or 2.32 mm of copper.

The data were analysed by the Pike-Alper method excluding surviving fraction values above 0.2. For independent values of N this gave $D_0=274.2$ rad (247.8–306.8) and $N=12.1$ (5.53–26.5) for the hypoxic data and $D_0=134.9$ rad (104.7–189.5) with $N=1.88$ (0.398–8.93) for the oxic data. The 95% confidence limits are given in parentheses. Analysis with an assumed common value for N gave D_0 values of 296.8 rad and 109.6 rad for the hypoxic and oxic data respectively with a common N value of 6.87. However, the F ratio was 7.55 which corresponds to a probability of between 0.01 and 0.05

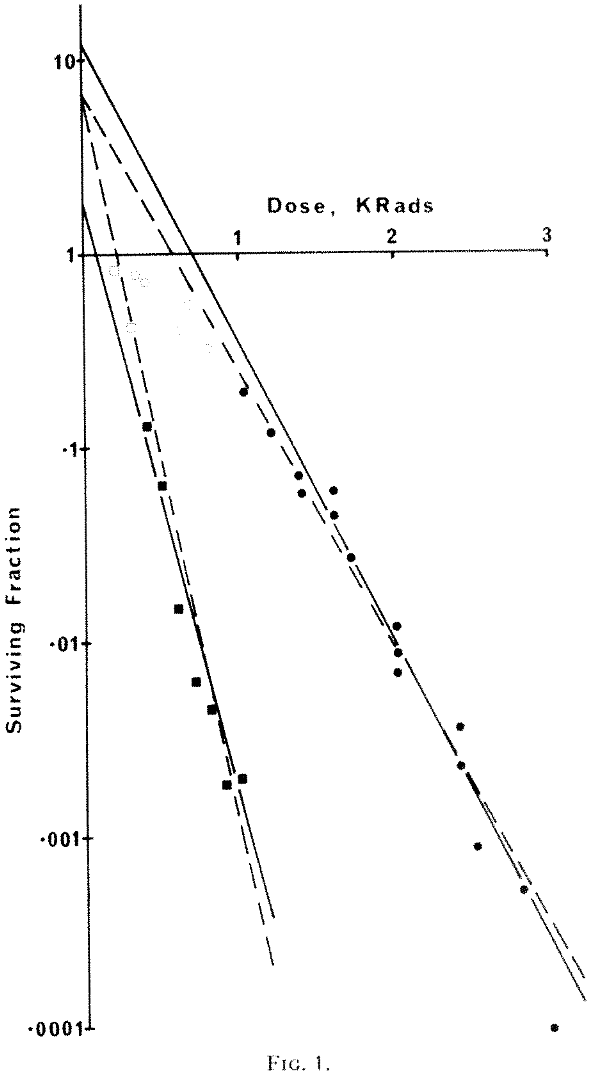


FIG. 1.

Results of conventional Pike-Alper analysis. Open symbols were those excluded from the analysis. The squares and circles represent oxic and hypoxic data respectively. Uninterrupted lines, independent values of N; dashed lines common value of N.

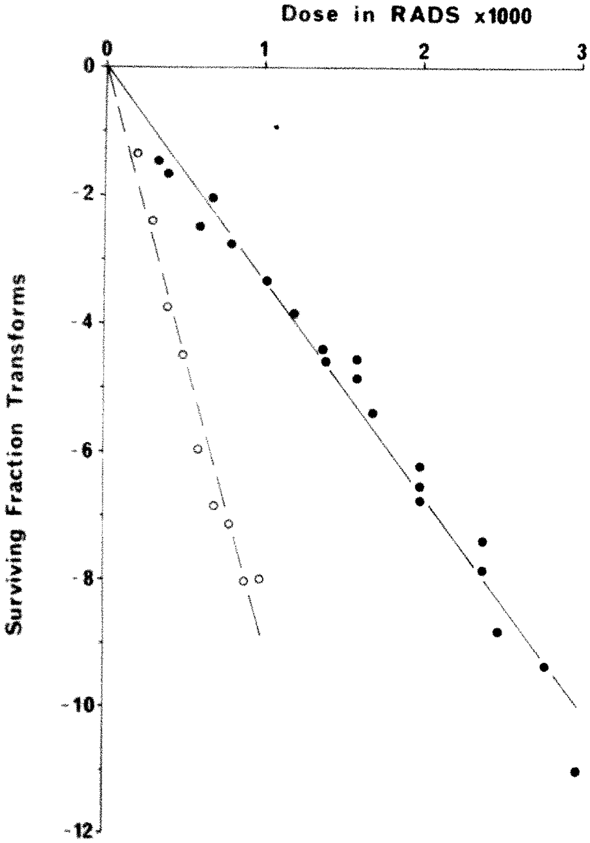


FIG. 2.

Regression lines fitting the transformed oxic (open symbols) and hypoxic (closed symbols) data.

(on 1 and 25 degrees of freedom) that the difference in N values between the 3 and 4 parameter hypotheses could have arisen by chance. On this basis we must reject the common N hypothesis and conclude that oxygen is not truly "dose-modifying" in this case. These results are shown graphically in Fig. 1 where the open symbols represent the points excluded from analysis.

The results of the linear transform analysis outlined in the present paper are shown in Fig. 2. The open and closed symbols represent the oxic and hypoxic data respectively. The survival curve parameters were $N=5.52$ and $D_0=114.0$ rad for the oxic data, and $N=6.06$ with $D_0=301.0$ rad for the hypoxic data. It will be noted that both regressions pass through the origin although the values of N are different.

Neither of these independent linear transform analyses produced a minimum residual sum of squares with the constraint of intersecting the origin. However, the F ratios calculated by comparing the

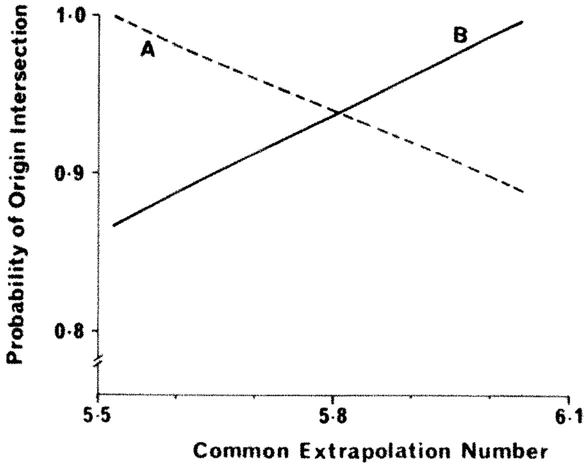


FIG. 3.

Probabilities of intersection of the origin for the regressions of the oxic (curve A) and the hypoxic (curve B) data plotted against the common extrapolation number.

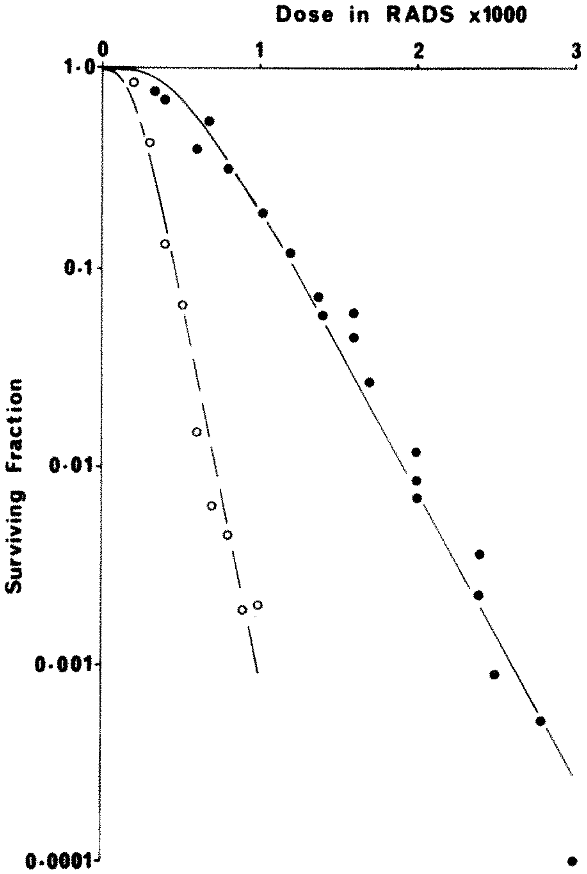


FIG. 4.

Conventional display of the data, symbolic representation as for Fig. 2. Common $N=5.8$, oxic $D_0=113.9$ rad, hypoxic $D_0=301.1$ rad.

TABLE I

COMPARISON OF RESULTS FROM THE LINEAR TRANSFORM AND PIKE-ALPER METHOD FOR THE THREE PARAMETER HYPOTHESIS, COMMON VALUE FOR N. THE 95% CONFIDENCE LIMITS ARE GIVEN IN PARENTHESES.

	Linear Transform			Pike-Alper		
	D_0	N	OER	D_0	N	OER
Hypoxic	301.1 (270→341)	5.80 (3.2→10.8)	2.64	296.8 (266→333)	6.87 (3.2→14.6)	2.71
Oxic	113.9 (102→129)			109.6 (98→125)		

unexplained variances from the computations for intersection of the origin and minimum residuals were 1.025 and 1.38 respectively for the hypoxic and oxic data. In both cases $p > 0.2$ which indicates that the constraint of intersecting the origin does not, in either set of data, produce significantly different results compared with those obtained by calculating for minimum residuals.

The second phase of the analysis, assuming a common value for N, was also carried out and Fig. 3 shows the probabilities of intersection of the origin for both sets of data plotted against the common extrapolation number. The two curves cross at a probability of 0.939 with a common value for N of 5.803. Comparison of the unexplained combined total variance from the unconstrained individual analyses (giving absolute minimum residuals) with the combined unexplained variances from the four and three parameter hypotheses respectively gave F ratios of 1.211 and 1.215, $p > 0.2$ in both cases. A similar comparison directly between the four and three parameter hypotheses gave an F ratio very close to 1.0, $p > 0.2$. Thus, in contrast to the Pike-Alper analysis, the linear transform predicts that a common N value is valid for these data and we can conclude that oxygen is "dose-modifying" in this case.

The table summarizes the results of the three parameter hypothesis obtained with both methods, and Fig. 4 shows the conventional display of the data and theoretical curves calculated with the linear transform parameters given in the table.

DISCUSSION

It is interesting that both the linear transform and the Pike-Alper analyses have produced almost identical results when a common value for N is assumed. However, the linear transform method predicts compatibility with the assumption of a true oxygen "dose-modification" for these data whereas the Pike-Alper method does not. This discrepancy is due to the exclusion of data on the shoulder in the latter analysis which causes a bias towards the lower survival levels. In the analysis with independent N values this produced a decreased D_0 and an increased N for the hypoxic data, and the reverse effect with the oxic data, compared with the linear transform results where all the data were included in the analysis. By "looking along" the regression lines in Fig. 2 it can be seen that both sets of data points tend to scatter in a curve about their respective regression lines. Hence, the results obtained by the Pike-Alper method will be dependent upon the subjective assessment of which points to exclude. It is also possible that a model of the type pioneered by Neary (1965) and developed by Chadwick and Leenhouts (1973) would be more appropriate for the hypoxic data.

Gilbert (1974) has also proposed a transform of mortality probabilities which is essentially a multi-target curve. For large values of N this transform is linear to lower radiation doses than the conventional log of survival, but it does extrapolate to a non-zero value on the ordinate. Hence, its use for the analysis of cell survival data still requires that a subjective assessment be made about which points to exclude from the analysis. Blackett and Scott (1976) have attempted to overcome this problem by the use of a "Monte Carlo" approach. Their method generates a number of synthetic survival curves for any particular model, in which random variation is introduced into the parameters of the equation. Thus, if the multi-target model is assumed, it is possible to obtain frequency distributions for the values of N and D_0.

The transform presented here also attempts to overcome some of the problems by enabling all data to be included in the analysis. Furthermore, the transform causes a vertical "expansion" of the shoulder of the theoretical curve which may make it possible to analyse with more precision data obtained at lower, and more clinically relevant, radiation doses.

Summary

A completely linear transform of the multi-target survival curve is presented. This enables all data, including those on the shoulder region of the curve, to be analysed. The necessity to make a subjective assessment about which data points to exclude for conventional methods of analysis is, therefore, removed. The analysis has also been adapted to include a "Pike-Alper" method of assessing dose modification factors. For the data cited this predicts compatibility with the hypothesis of a true oxygen "dose-modification" whereas the conventional Pike-Alper analysis does not.

Acknowledgments

I would like to thank Professor N. M. Bleehen and Dr. I. Har-Kedar for permission to use unpublished experimental data as the examples, and Dr. D. K. Bewley who carried out the conventional "Pike-Alper" analysis.

REFERENCES

Alper, T., Gilles, N. E., and Elkind, M. M., 1960. The sigmoid survival curve in radiobiology. *Nature, 186*, 1062–1063.

Blackett, N. M., and Scott, O. A. C., 1976. A Monte Carlo approach to the accuracy of cell survival curves. *British Journal of Radiology, 49*, 464–467.

Chadwick, K. H., and Leenhouts, H. P., 1973. A molecular theory of cell survival. *Physics in Medicine and Biology, 18*, 78–87.

Gilbert, C. W., 1974. A double minus log transformation of mortality probabilities. *International Journal of Radiation Biology, 25*, 633–634.

Neary, G. J., 1965. Chromosome aberrations and the theory of RBE. *International Journal of Radiation Biology, 9*, 477–502.

Pike, M. C., and Alper, T., 1964. A method for determining dose modification factors. *British Journal of Radiology, 37*, 458–462.

Rockwell, S., and Kallman, R. F., 1973. Cellular radiosensitivity and tumour radiation response in the EMT6 tumour cell system. *Radiation Research, 53*, 281–294.

Book reviews

Skeletal projections for diagnostic radiology. By Anders Movin and Ulf Karlsson, pp. 264, 1975. (J. B. Lippincott Co, U.S.A; distributed in U.K by Blackwell Scientific Publications, Oxford), £15·20.

The opening sections of this book deal with basic anatomical descriptions and an explanation of the various terms used in radiography relating to body planes, directions and positions and body movements. The technical aspects of X-ray production and the radiographic factors which influence the final image are also briefly considered.

The main body of the book displays radiographic positions and techniques in a very clear manner utilizing combined radiographs and line drawings. These are covered in sequential anatomical regions preceded by a most useful section on special aspects, bridging the gap between technical and clinical terminology. The book is completed by an appendix providing combinations of radiographic projections for use in various types of injury and finally by a glossary of medical terminology.

This slim handbook was written with a wide readership in mind, "radiologists, residents, assistants of radiology and radiologic technologists". It is always difficult to cater for the needs of the specialist and the generalist in a field such as this. This book is not likely to replace the standard reference work on positioning and radiography already available in this country. However, the book does contain a great deal of valuable practical information in an easily usable form. However, radiography students should note that some of the X-ray projections are not standard to this country and this might be misleading for those taking examinations.

This book is recommended as a reference source for the larger X-ray department, particularly if it could be available to orthopaedic residents, casualty officers as well as students of radiography.

T. Hayden.

Nuclear Ophthalmology. Edited by M. N. Croll, L. W. Brady, P. Carmichael and R. J. Wallner, pp. xi+284, 1976 (John Wiley & Sons, Chichester), £19·25.

This book is a series of 24 papers presented to a symposium on nuclear ophthalmology held at Hahnemann Medical College in 1975. This is not a subject generally covered well by standard nuclear medicine or ophthalmology texts and is the only justification for the book and presumably the justification for the symposium. It is a book which is worth knowing about as a starting point for someone with the general intention of applying nuclear medicine techniques to ophthalmology. In this case, flicking through the pages might result in some ideas but the coverage is so superficial that original publications would be required very quickly. There are several good papers on the differentiation of benign from malignant melanotic lesions using P^{32} and direct contact detectors, a technique which has been available since the early fifties. Otherwise it is mostly padding; a paper on instrumentation by Dr. Craig Harris, which is below his usual illuminating standard, a general paper on the principles of tumour detection, an interesting but irrelevant paper on Grave's ophthalmopathy, and a series of papers on dynamic scintigraphy, with $^{99}Tc^{m}$, of the orbit containing mainly idiosyncratic case reports and no clear teaching points. The chapter on detection of metastases from eye tumours was medical student standard and contained images which most of us would not let out of the department let alone publish them! I did like the short paper on detecting posterior uptake of P^{32} by measuring the Cerenkov effect in the vitreous—has any more been heard of this idea since? The only useful technique in ophthalmology, *i.e.*, lacrimal drainage studies was dealt with too superficially to be really useful. I am sure that the symposium on nuclear ophthalmology was good but unfortunately the publication is not, and cannot be recommended.

M. N. Maisey.

1978, *British Journal of Radiology*, *51*, 539–541

JULY 1978

Case reports

Essential osteolysis of carpal and tarsal bones

By P. H. Amin, D.M.R.D., F.R.C.R.,* and A. N. W. Evans, M.B., Ch.B.

Departments of Pediatric Radiology and Paediatrics, General Hospital, Southampton, Hants. SO9 4XY

(*Received August, 1977 and in revised form October, 1977*)

Essential osteolysis of carpal and tarsal bones is a rare disease which causes progressive shrinkage of these bones and may be associated with nephritis and hypertension. A familial variant has been reported. It has been variously described as essential osteolysis with nephropathy (Torg and Steel, 1968), familial osteolysis of carpal and tarsal bones (Gluck and Miller, 1972), osteoarticular changes in a case of essential osteolysis (Lagier and Rutishauser, 1965), hereditary osteolysis with hypertension and nephropathy (Shurtleff, *et al.*, 1963), carpal and tarsal agenesis with features of essential hereditary osteolysis (McManus *et al.*, 1972), bilateral carpal necrosis (Caffey, 1973) and hereditary multicentric osteolysis with recessive transmission (Torg *et al.*, 1969).

The syndrome is characterized by progressive shrinkage of bones of the hands and feet. Elbows,

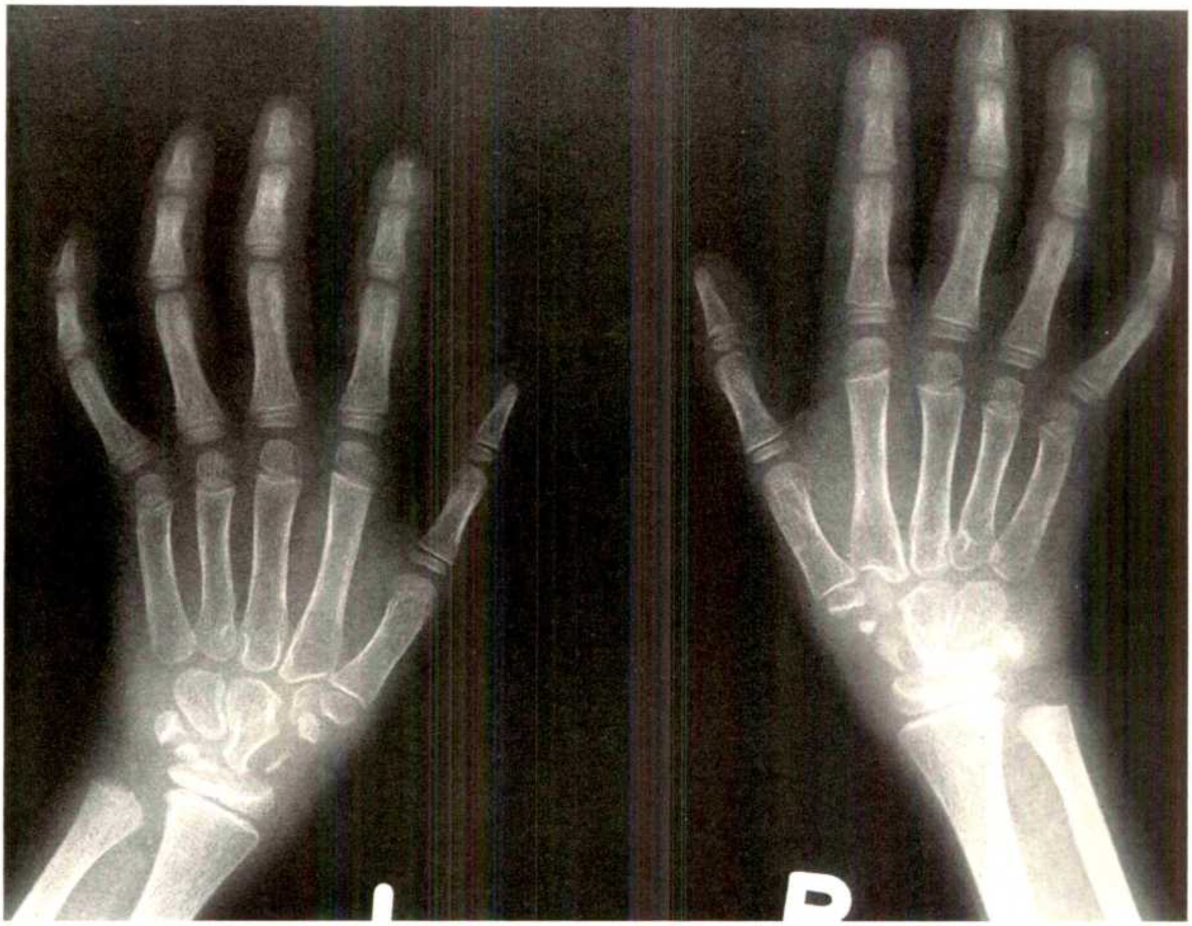


FIG. 1.

Carpal bones are affected by irregular erosions which have resulted in crenation of normal outlines of these bones. The epiphyseal plate is normal.

---

*Present address: Department of Radiology, University of Illinois Hospital, 840 South Wood Street, Chicago, Illinois, 60680.

knees and hips may also be involved (Lagier and Rutishauser, 1965; Torg and Steel, 1968; McManus, *et al.*, 1972). Tapering resorption of the ungual tufts and clavicles has been described by Lagier and his colleagues (1965). The patients may have scoliosis (Kohler *et al.*, 1973; Lagier and Rutishauser, 1965).

CASE REPORT

A boy aged six years complained of swelling and tenderness of both wrists for six months. Pain was precipitated by movement. There was no history of trauma. He had been seen at one month of age because of widely separated cranial sutures but the follow-up was uneventful. Obstetric history was unremarkable and the birth weight was 3.5 kg. His mother was Rhesus negative but did not require treatment.

On examination, the wrists were swollen and slightly tender but no other abnormality was found. The B.P. was 100/60; blood count, Hb, ESR, blood chemistry including blood urea, Ca, P., alkaline phosphatase and electrophoresis were normal. Urine examination was also normal. Radiographs of the wrists, elbows, hips, knees and ankles showed that the abnormalities were confined to the wrists only. The wrists showed well-defined erosions of the carpal bones and ulnae (Fig. 1). The bases of the index, middle and ring finger metacarpals showed similar but smaller erosions. Bone age was normal for the patient's chronological age. A diagnosis of the syndrome of osteolysis of the carpal bones was made. The parents, siblings and grandmother were examined. No relevant abnormality was found either on clinical or radiological examinations. There is no evidence of a familial link at this time. Radiographs of the hands after intervals of 12 and 24 months showed that a further loss of substance of the carpal bones had taken place.

DISCUSSION

The disorder has its onset in childhood and is usually first detected around the age of five years. The early manifestations resemble an acute arthritis with pain and swelling of wrists and ankles. Progress is generally slow and protracted but relatively asymptomatic. Changes in cartilage and bone show gradual deterioration until the second decade when the disorder tends to stabilize. The degree of disability in adult life varies. The erosion and shrinkage of cartilage and bone produce crippling joint deformities. Atrophy of the muscles of forearms and legs (Lagier and Rutishauser, 1965) and Dupuytren-like contractures have been noted (Gluck and Miller, 1972; Shurtleff *et al.*, 1963).

Erosion and necrosis of cartilage and bone is associated with rheumatoid arthritis, Raynaud's disease, scleroderma, Gorham's disappearing bone disease and post-traumatic avascular bone necrosis. The clinical progress and biochemical studies set apart these disorders from the syndrome of essential osteolysis of carpal and tarsal bones. The pattern of bone involvement and biochemical aberrations distinguishes these cases from acid mucopolysaccharidosis. Gluck and his associates (1972) have suggested that the syndrome of osteolysis of carpal and tarsal bones may be a variant of the group of disappearing bone diseases.

Associated renal abnormalities and hypertension have been described in the literature (Lagier and Rutishauser, 1965; Shurtleff *et al.*, 1963; Derot *et al.*, 1961; Marie *et al.*, 1963; Thieffry and Sorrel-Dejerine, 1958). Biochemical aberrations in these patients are due to the chronic renal disease. The renal component is generally progressive and may prove fatal (Torg and Steel, 1968).

There are numerous reports of familial association of this disorder. The families studied showed the mode of inheritance as autosomal dominant (Shurtleff *et al.*, 1963; Thieffry and Sorrel-Dejerine, 1958). A recessive mode of transmission was noted by Torg and associates in the family they studied (Torg *et al.*, 1969).

The case reported here and some of the other cases described in the literature (Lagier and Rutishauser, 1965; Torg and Steel, 1968; Marie *et al.*, 1963; Derot *et al.*, 1961) have no familial component and to date, we have no evidence of renal involvement in our patient.

The aetiology remains unknown. Biopsy and necropsy studies have failed to provide a definite clue as to the nature of this disorder. Shurtleff and associates described vascular abnormalities on histology. However it has no resemblance to the histological findings in Gorham's massive osteolysis. Lagier and Rutishauser described features consistent with the slow, sluggish progress of this disorder. Their very extensive necropsy study did not reveal a definite clue as to the causation. Histological examination showed no evidence of synovial involvement, inflammatory reaction, or of vascular changes in articular or periarticular tissues.

RADIOLOGY

The carpal bones are affected by irregular erosions which result in crenations of the normal outlines of these bones. The margins of the crenations are well defined and have a sclerotic edge in places (Fig. 2). The zone of transition between normal and affected bone is very narrow. Small erosions of the bases of the metacarpal bones result in apparent widening of the joint spaces. The interphalangeal joints and the ungual tufts are normal at this stage. There is some osteoporosis of bones.

The changes may progress to fragmentation, sequestration, necrosis and complete disappearance of bone. Bone involvement is bilateral and may be symmetrical. Tapering erosions have been noted on the adjoining long bones, such as radius and ulna (Torg and Steel, 1968; Kohler *et al.*, 1973). The

1978, *British Journal of Radiology*, *51*, 541–543

JULY 1978

Case reports

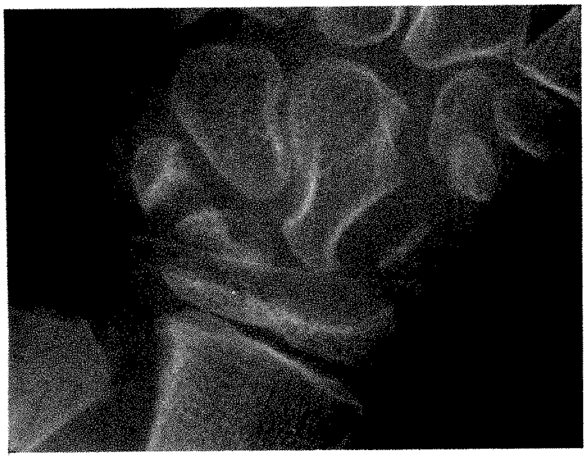


FIG. 2.

Magnified view of carpal bones showing irregular erosion. The margins of crenations are well defined and have a sclerotic edge.

epiphyseal plates are normal. The long bones may appear hypoplastic. Radiographic changes offer a valuable clue to the diagnosis of the syndrome of essential osteolysis of carpal and tarsal bones.

ACKNOWLEDGMENT

We wish to thank Dr. I. Hyde for his considerable help and encouragement in the writing of this paper. Mrs. Victoria Catalini kindly typed the manuscript.

REFERENCES

CAFFEY, J., 1973. Bilateral carpal necrosis, *Pediatric X-ray Diagnosis, Vol. II*, 1179–80 (Year Book Publishers, Inc.)

DEROT, M. R., RATHERY, M., ROSSELIN, J., and CATELLIER, C., 1961. Acro-ostéolyse du carpe, pied creux, scoliose et strabisme chez une jeune fille atteinte d'une insuffisance rénale, *Bulletins et Memoires de la Societé Medicale des Hopitaux de Paris*, *77*, 223–228.

GLUCK, J., MILLER, J. J., 1972. Familial osteolysis of carpal and tarsal bones *The Journal of Pediatrics*, *81*, 506–510.

KOHLER, E., BABBIT, D., HUIZENGA, B., GOOD, T., 1973. Hereditary osteolysis. *Pediatric Radiology*, *108*, 99–105.

LAGIER, R., RUTISHAUSER, E., 1965. Osteoarticular changes in a case of essential osteolysis. *The Journal of Bone and Joint Surgery*, *47B*, 339–353.

MARIE, J., LÉVÊQUE, B., LYON, G., BEBE, M., and WATCHI, J., 1963. Acro-ostéolyse essentielle compliquée d'insuffisance rénale d'évolution fatale. *Presse Medicale*, *71*, 249–252.

MCMANUS, L. F., BALLARD, C. A., WALTON, S., and OMER, G. E., 1972. Carpal and tarsal agenesis with features of essential and hereditary osteolysis. *Journal of Bone and Joint Surgery*, *54A*, 1099–1104.

SHURTLEFF, D. B., SPARKES, R. S., CLAWSON, D. K., GUNTHEROTH, W. G., and MOTTET, N. K., 1963. Hereditary osteolysis with hypertension and nephropathy. *Journal of the American Medical Association*, *188*, 363–368.

THIEFFRY, S., and SORREL-DEJERINE, J., 1958. Forme spéciale d'ostéolyse essentialle héréditaire et familiale à stabilisation spontanée, survenant dans l'enfance. *Presse Medicale*, *66*, 1858–1861.

TORG, J. S., STEEL, H. H., 1968. Essential osteolysis with nephropathy. *The Journal of Bone and Joint Surgery*, *50A*, 1629–1638.

TORG, J. S., DIGEORGE, A. M., KIRKPATRICK, J. A., and TRUJILLO, M. M., 1969. Hereditary multicentric osteolysis with recessive transmission: a new syndrome. *Journal of Pediatrics*, *75*, 243–252.

Complications of "Chiba" needle transhepatic cholangiography

By H. Moskowitz, M.D., C. Polivy, M.D., A. W. Hackford, M.D., N. Mann, M.D., and M. Josel, M.D.

Departments of Radiology, Surgery and Medicine, Mount Sinai Hospital, 500 Blue Hills Avenue, Hartford, Connecticut 06112, U.S.A.

(*Received September, 1977 and in revised form January, 1978*).

In the forty years since its inception transhepatic cholangiography has been a valuable adjunct in the diagnosis of jaundice of uncertain aetiology. Recently the procedure has been modified by the use of a thin, flexible needle, the "Chiba" needle, which decreases the major complications following the use of sheathed needles and catheters. The following case records a complication encountered following "Chiba" needle transhepatic cholangiography.

CASE REPORT

A fifty-year-old Jamaican female presented to Mount Sinai Hospital with massive haematemesis and jaundice. She had been hospitalized four months previously, at another hospital, where a 50% gastrectomy and Billroth II anastomosis was performed, for a duodenal ulcer with gastric outlet obstruction. One month later a subhepatic collection was drained. The patient was well until two weeks prior to admission, when she noted increasingly dark urine and black, tarry stools. In the twenty-four hours prior to admission, she vomited both coffee-ground material and frank blood.

On admission the patient was in shock and clinically icteric. On physical examination a palpable mass in the epigastrium, extending to the right upper quadrant and measuring 10 × 8 cm., was felt. The haemoglobin was 4.7 gm and the heamatocrit 14.9%. Liver function tests revealed an SGOT of 137 I.U. (normal 7–21), alkaline phosphatase 597 I.U. (normal 6–100), direct bilirubin 8.3 mg./100 ml., and cholesterol 350 mg.%. Prothrombin was 100%, and the PTT was within normal range.

Endoscopy failed to reveal a bleeding site. After receiving blood and packed cells, the patient's condition stabilized.

Abdominal ultrasound (Fig. 1) revealed dilated bile ducts and a cystic mass in the region of the pancreatic head. A "Chiba" needle transhepatic cholangiogram, using the right lateral approach, showed a dilated intrahepatic biliary system with the common bile duct markedly dilated and the

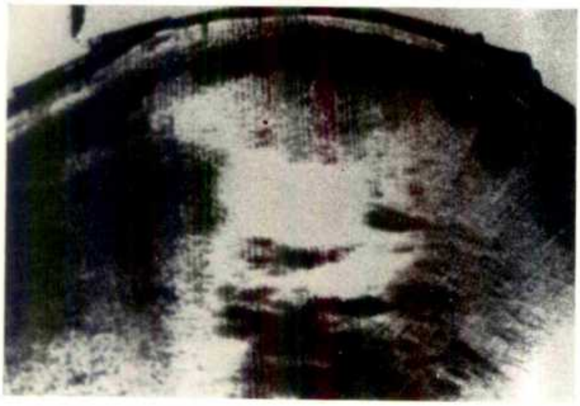


Fig. 1.

Grey-scale ultrasound reveals a cystic mass in the region of the head of the pancreas with associated, dilated intrahepatic ducts.

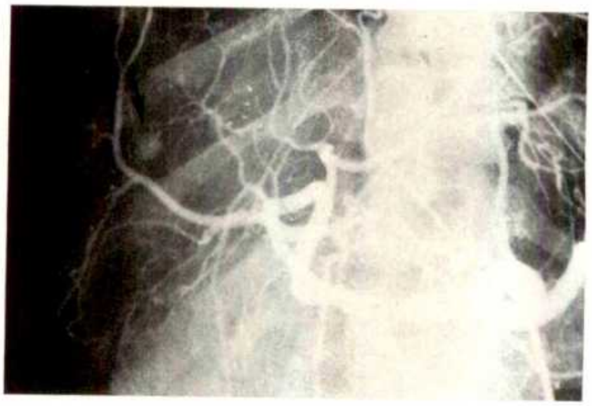


Fig. 3.

Coeliac arteriogram reveals extravasation of contrast from a small branch of the right hepatic artery just at the site of the previous transhepatic cholangiogram.

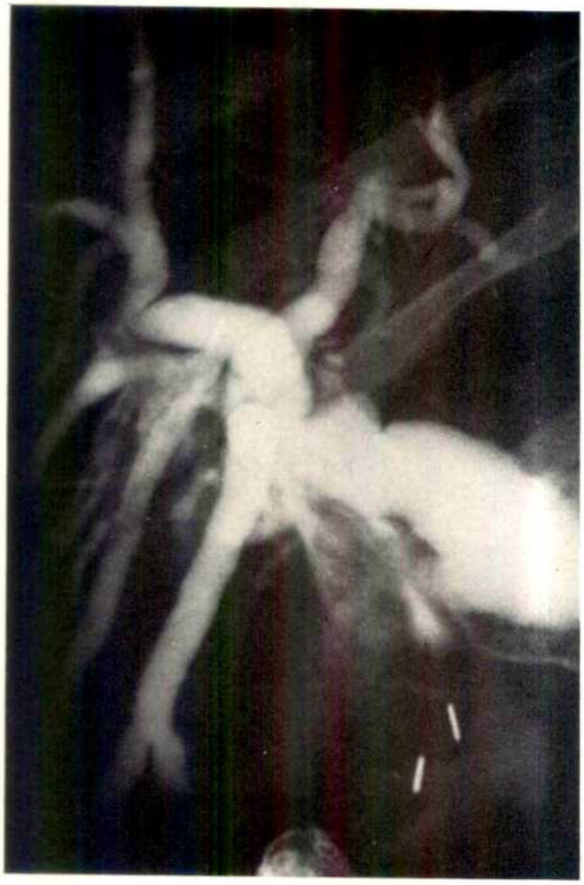


Fig. 2.

Skinny needle transhepatic cholangiogram reveals dilated intrahepatic ducts with a dilated common hepatic duct down to a mass in the region of the head of the pancreas.

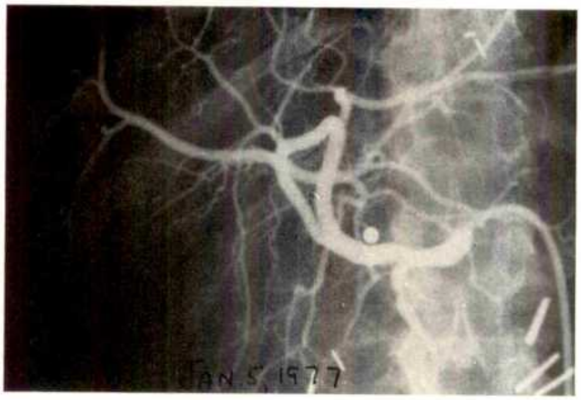


Fig. 4.

Repeat coeliac arteriography six days later fails to reveal any extravasation of contrast from the hepatic artery. There seems to be further encasement of the gastroduodenal artery by tumour.

distal end deviated medially with a tapered distal end (Fig. 2). Selective superior mesenteric and coeliac arteriography performed on the following day revealed the gastroduodenal artery to be displaced medially and encased. The superior and inferior pancreatico-duodenal arteries were markedly displaced round a cystic mass in the region of the head of the pancreas. In the right lobe of the liver, arising from a small branch of the right hepatic artery, a puddle of contrast could be seen in the liver parenchyma representing contrast extravasation (Fig. 3). This was exactly at the site of the Chiba needle puncture.

On the sixth hospital day laparotomy was performed, an adenocarcinoma of the distal biliary tree was found ulcerating into the closed duodenal stump. The tumour involved the gallbladder, the liver and the previous surgical scar.

Six days later a decision was made to infuse chemotherapy. Repeat coeliac arteriography was performed. There seemed to have been further encasement of the gastroduodenal artery, and, at this time, the extravasation from the right hepatic artery was no longer visible (Fig. 4).

DISCUSSION

Traditionally, transhepatic cholangiography was performed only on patients who were scheduled for laparotomy due to possible complications of bile leakage and haemorrhage. Initially, the complication rate of the procedure was thought to be somewhere between 5 and 10% (Hines *et al.*, 1972); however, the use of polyethylene catheters reduced the complication rates to 4–8% (Gothlin and Tranberg, 1973; Lang, 1974; Burcarth and Nielbo, 1976).

Okuda *et al.*, (1974) demonstrated a marked reduction in complication rates by using a thin, flexible "Chiba" needle. Complications developed in less than 1% of the patients. The success rate of cannulating a dilated biliary tree with the "Chiba" needle has been close to 100%, while the rate for nondilated systems range from 60–89% (Okuda *et al.*, 1974; Redeker, *et al.*, 1975; Tabrisky, *et al.*, 1976; Pereiras *et al.*, 1976). There has been no report of vascular complications.

Angiography following needle puncture of the liver with larger needles or sheathed needles has demonstrated the formation of arterioportal shunts, occluded arteries, haematomas, and extravasation of contrast. These abnormalities occurred in a high percentage of cases if angiography was performed within one week of puncture (Hellekant 1976).

There have been no reported cases of vascular complication following "Chiba" needle cholangiography. In this case, selective superior mesenteric and celiac arteriography, performed two days following successful "Chiba" needle cannulation of a dilated biliary tree revealed contrast extravasation at the site of the liver puncture with the "Chiba" needle.

While the "Chiba" needle modification extends the usefulness of transhepatic cholangiography to both "medical" and "surgical" jaundice by eliminating the need for surgical stand by, this case suggests that the true complication rate may be higher than is now anticipated.

REFERENCES

BURCARTH, F. and NIELBO, N., 1976. Percutaneous transhepatic cholangiography with selective catheterization of the common bile duct. *American Journal of Roentgenology*, *127*, 409–412.

GÖTHLIN, J. and TRANBERG, K., 1973. Complications of percutaneous transhepatic cholangiography (PTC). *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *117*, 426–431.

HELLEKANT, C., 1976. Vascular complications following needle puncture of the liver. Clinical angiography. *Acta Radiologica* (*Diagn*), *17*, 209–222.

HINES, C. Jr., FERRANTE, W., DAVIS, W., TUTTON, R. A., 1972. Percutaneous transhepatic cholangiography. Experience with 102 procedures. *American Journal of Digestive Diseases*, *17*, 868–874.

LANG, E., 1974. Percutaneous transhepatic cholangiography. *Radiology*, *112*, 283–290.

OKUDA, K., TANIKAWA, K., EMURA, T., KURATOMI, S., JINNOUCHI, S., URABE, K., SUMIKOSHI, T., KANDA, Y., FUKUYAMS, Y., MUSHA, H., MORI, H., SHIMOKAWA, Y., YAKUSHIJI, F., MATSUURA, Y., 1974. Nonsurgical percutaneous transhepatic cholangiography – diagnostic significance in medical problems of the liver. *American Journal of Digestive Diseases*, *19*, 21–36.

PEREIRAS, R., JR., WHITE, P., DUSOL, M., IRVIN, G., HUTSON, D., LIEBERMAN, B., SCHIFF, E. R. 1976. Percutaneous transhepatic cholangiography utilizing the Chiba university needle. *Radiology*, *121*, 219–221.

REDEKER, A., KARVOUNTZIS, G., RICHMAN, R., and HORISAWA, M., 1975. Percutaneous transhepatic cholangiography. *Journal of the American Medical Association*, *231*, 386–387.

TABRISKY, J., LINDSTROM, R., HANELIN, L., PFISTERER, W. F., 1976, Chiba percutaneous transhepatic cholangiography. A valuable method for visualizing the nondilated biliary tract. *American Journal of Roentgenology*, *126*, 755–760.

Multicystic kidney—an example of bilateral involvement in an adult

By C. D. R. Flower, F.R.C.R., and P. G. Kitchener, M.R.C.P.

Department of Diagnostic Radiology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

(*Received November, 1977 and in revised form January, 1978*)

Multicystic kidney is a relatively common condition in infants. It should always be considered in the differential diagnosis of an abdominal mass at that age (Kyaw and Koehler, 1976). The condition may also be seen in adulthood when it presents as a non-excreting renal mass which may exhibit ring calcification on the abdominal radiograph and is invariably associated with an absent or atretic ureter and an absent or hypoplastic renal artery (Kyaw and Koehler, 1976). Bilateral multicystic disease also occurs (Greene *et al.*, 1971). It is normally incompatible with life and is therefore seldom brought to the attention of radiologists.

We wish to describe the urographic findings in an adult female who we believe exhibits the features of bilateral multicystic disease.

Case Report

A 26-year-old female first consulted her general practitioner in 1973 because of a urinary tract infection. She subsequently experienced frequency of micturition but did not present again until 1976 when a further urinary tract infection was proven and heavy proteinuria was noted. Her blood pressure was 160/100. Subsequent investigations revealed a blood urea of 32.3 mmol/l, a creatinine of 928 μmol/l and a creatinine clearance of 4 ml/min. No calcification was seen on the plain abdominal radiograph. Intravenous urography revealed two small kidneys. There was poor excretion of contrast medium by the right kidney but a deformed collecting system was delineated together with several lucent "cysts" particularly at the lower pole. The left kidney was poorly visualized but appeared to be replaced by multiple circular lucent defects resembling cysts (Fig. 1). At cystoscopy there was no evidence of a left ureteric orifice. The right ureteric orifice was normal and a right retrograde pyelogram was performed. Contrast medium filled the previously described deformed pelvicalyceal system, together with the majority of the "cysts" in the lower pole. A short tight stricture was also demonstrated at the junction of the middle and upper thirds of the ureter (Fig. 2).

She was managed conservatively with a low protein and low potassium diet and her blood pressure was well controlled. For a variety of personal and social reasons she was not dialysed or offered transplantation, and she died in April 1977. Regrettably, a post-mortem was not performed.

Visualization of the left kidney with its cystic replacement is probably related to total body opacification. We believe that these appearances in association with the absence of the left ureter substantiate the diagnosis of multicystic kidney on the left.

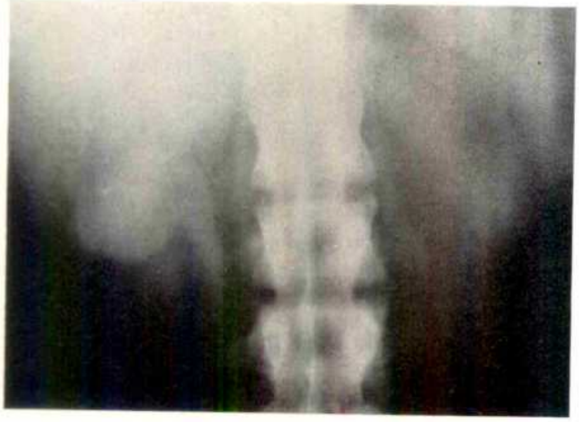


Fig. 1.

Nephrotomogram following injection of contrast medium. The left kidney is faintly opacified and a cyst is seen in the lower pole. On the right there is a deformed collecting system with a "cystic" space in the lower pole.

Contralateral renal disease is well documented in this condition, occurring in approximately 30% of all cases (Greene *et al.*, 1971). Pelviureteric and ureteric abnormalities, together with anomalies of rotation have all been described (Greene *et al.*, 1971;

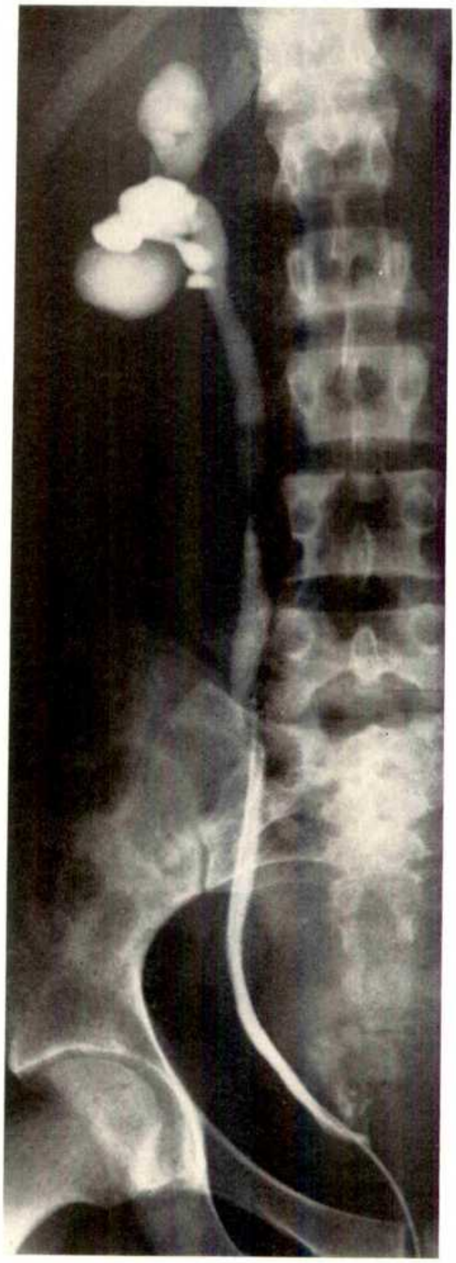


Fig. 2.

Right retrograde pyelogram demonstrating the deformed collecting system and ureteric stricture (adjacent to L.4). The lower pole "cyst" seen at urography has filled with contrast medium.

Pathak and Williams, 1964). There has been considerable disagreement as to whether the primary abnormality in this disorder occurs with development of the ureteric bud or metanephric blastema. The presence of obstructive contralateral lesions has led some authors to suggest an obstructive aetiology for unilateral multicystic kidney (Griscom *et al.*, 1975) and this view has been reiterated by Felson and Cussen (1975). There is much to support this point of view. Renal dysplasia identical to that seen in multicystic kidney may develop secondary to varying degrees of ureteric or outlet obstruction in infants, as in posterior urethral valves and in renal moieties associated with ectopic ureters and ureteroceles. A condition closely resembling multicystic kidney was produced experimentally in lambs by Beck (1971) by means of ureteric ligation *in utero* during the first half of gestation.

In our patient, retrograde pyelography on the right clearly demonstrated a communication between some of the renal "cysts" and the ureter. We suggest that the ureteric narrowing may have been responsible for the calyceal anomalies. Whatever the truth of this hypothesis, our case emphasizes the importance of remembering the possibility of abnormalities in the contralateral kidney or ureter when multicystic kidney is diagnosed.

REFERENCES

BECK, A. D., 1971. The effect of intra-uterine urinary obstruction upon the development of the fetal kidney. *Journal of Urology*, *105*, 784–789.

FELSON, B., and CUSSEN, L. J., 1975. The hydronephrotic type of unilateral congenital multicystic disease of the kidney. *Seminars in Roentgenology*, *10*, 113–123.

GREENE, L. F., FEINZAIG, W., and DAHLIN, D. C., 1971. Multicystic dysplasia of the kidney: with special reference to the contralateral kidney. *Journal of Urology*, *105*, 482–487.

GRISCOM, N. T., VAWTER, G. F., and FELLERS, F. X., 1975. Pelvoinfundibular atresia: the usual form of multicystic kidney. *Seminars in Roentgenology*, *10*, 125–131.

KYAW, M. M., and KOEHLER, P. R., 1976. In *Cystic Diseases of the Kidney*, ed. K. D. Gardner, Jnr., pp. 115–123 (John Wiley and Sons, New York).

PATHAK, I. G., and WILLIAMS, D. I., 1964. Multicystic and cystic dysplastic kidneys. *British Journal of Urology*, *36*, 318–331.

Visualization of abnormal adrenal uptake of 19-iodocholesterol in Conn's syndrome

By D. M. Thomson, Ph.D., F.Inst.P., P. Dovey, D.M.R.D., F.R.C.R., and J. B. Davis, M.Sc.*

Physics Department, Mount Vernon Hospital, Northwood, Middlesex

(*Received June, 1977 and in revised form February, 1978*)

Localization of adrenal tumours using an intravenous dose of 19-iodocholesterol labelled with ^{131}I is well known (Beierwaltes *et al.*, 1974; Britton *et al.*, 1975, 1976; Conn *et al.*, 1972; Lieberman *et al.*, 1971; Sutton, 1975; Trocone *et al.*, 1977). A suitable thyroid blocking agent is administered and followed by the injection of the radiopharmaceutical. About three days later, the uptake is imaged using a rectilinear scanner or a gamma camera. Routine liver and kidney scans are carried out at the same time using different isotopes. This enables these organs to be localized and ^{131}I uptake in the adrenals can be distinguished from uptake elsewhere. Many reports (Beierwaltes *et al.*, 1974; Britton *et al.*, 1975, 1976; Conn *et al.*, 1972; Sutton, 1975) emphasize the value of "computer-assisted scintigraphy" as a means of subtracting unwanted uptake by image processing techniques. This requires expensive facilities not available at many centres. The purpose of this note is to report a case in which a very worthwhile adrenal scan was obtained without data processing. The necessary background subtraction was very effectively provided by administering a strong laxative to the patient and repeating the scan after a further three days.

CASE HISTORY

A 50-year-old woman presented with systemic hypertension of 15 years' duration. Her serum potassium ranged between 2 and 2.5 mmol/l, her serum aldosterone under basal conditions was six to seven times greater than normal, and her plasma renin was suppressed. The diagnosis of Conn's syndrome appeared conclusive. The surgeon wanted to know to which side his attention should be directed.

Three days after an intravenous injection of 2 mCi of ^{131}I-19-Iodocholesterol the patient was scanned using a rectilinear scanner (Picker Magnascanner V). A liver scan using 2 mCi of ^{99}Tc^{m} sulphur colloid, and a kidney scan using 2 mCi of ^{99}Tc^{m} DTPA, were carried out at the same time. The expected location of the adrenal glands could readily be established by superimposing the various scan images, which were produced on X-ray film, on a standard viewing box.

The first ^{131}I scan showed some indication of increased uptake in the left adrenal region, but the picture was obscured and confused by uptake in the colon and liver

---

*Present address: Service de Médicine Nucléaire, Hôpital Cantonal, Bertigny, 1700 Fribourg, Switzerland.

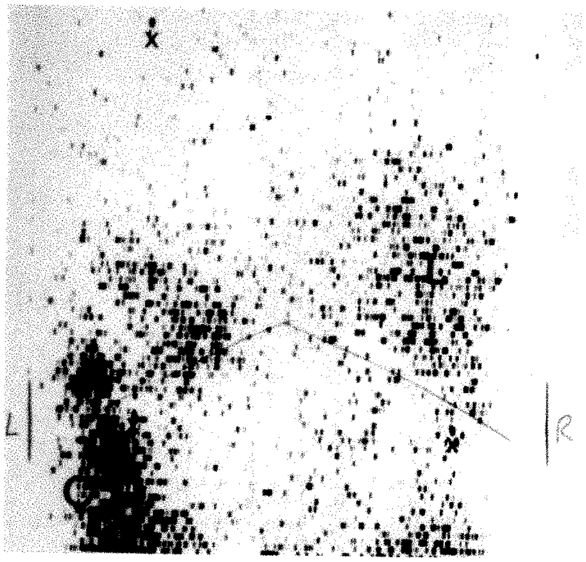


FIG. 1.

Three-day scan. Increased uptake in the left adrenal region, but this is obscured by uptake in the colon (C) and the liver (L). X = skin marks used for reference.

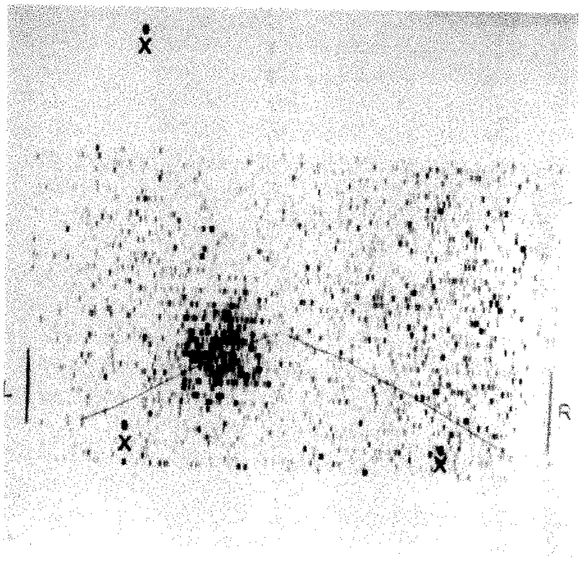


FIG. 2.

Six-day scan. After a dose of laxative, uptake in the left adrenal is clearly shown, activity in the surrounding tissue having fallen to background level. X = same skin marks.

(Fig. 1). At this point, the patient was advised to take a strong laxative and a repeat scan was done after a further three days. Uptake in the colon and liver was then found to have fallen to background levels, leaving clear evidence of increased uptake only in the region of the left adrenal gland (Fig. 2); this was entirely consistent with the presence of an adrenal tumour on this side.

Subsequently, the patient underwent left adrenalectomy. Prior to surgery both adrenals were imaged by ultrasound. This confirmed the presence of tumour on the left side. The right adrenal showed no abnormality.

At surgery the right adrenal was difficult to examine because of an anatomical variant, in that it was separated from the upper pole of the kidney and tucked up under the diaphragm. The left adrenal gland (4 × 2 cm) had a 2 cm nodule mid-way along, compressing the cortex, and a second 4.5 cm diameter nodule, also compressing the cortex, closely adjacent to the first. The histology confirmed a diagnosis of adrenocortical adenomas.

COMMENT

Centres without data processing facilities may, in the past, have hesitated to undertake adrenal scanning in view of the emphasis in the literature on the problem of background subtraction. This case seems to demonstrate that management of the patient may sometimes enable one to get very useful adrenal scans without having to resort to the computer.

ACKNOWLEDGMENT

We are grateful to Dr. E. J. Knight of Bushey and District Hospital for allowing us to report on one of his patients, and to Mr. G. L. Bunton, F.R.C.S., of University College Hospital, London, for kindly providing a report on the surgical and histological findings in this case.

REFERENCES

BEIERWALTES, W. H., STURMAN, M. F., RYO, U., and ICE, R. D., 1974. Imaging functional nodules of the adrenal glands with ^{131}I-19-iodocholesterol. *Journal of Nuclear Medicine, 15*, 246–251.

BRITTON, K. E., MYERS, M. J., BLUHM, M. M., and GOODWIN, T. J., 1975. *Early adrenal visualisation using subtraction techniques.* Paper presented at the Third Annual Meeting of the British Nuclear Medicine Society, London, March 20–21, 1975.

BRITTON, K. E., GOODWIN, T. J., PEART, W. S., and SNELL, M. E., 1976. Adrenal aldosterone-producing adenoma: use of colonic potential in diagnosis and substraction scanning technique for localisation. *British Medical Journal, 2*, 11–14.

CONN, J. W., MORITA, R., COHEN, E. L., BEIERWALTES, W. H., MCDONALD, W. J., and HERWIN, K. R., 1972. Primary aldosteronism. Photoscanning of tumours after administration of ^{131}I-19-iodocholesterol. *Archives of Internal Medicine, 129*, 417–425.

LIEBERMAN, L. M., BEIERWALTES, W. H., CONN, J. W., ANSARI, A. N., and NISHIYAMA, H., 1971. Diagnosis of adrenal disease by visualisation of human adrenal glands with ^{131}I-19-iodocholesterol. *The New England Journal of Medicine, 285*, 1387–1393.

SUTTON, D., 1975. The radiological diagnosis of adrenal tumours. *British Journal of Radiology, 48*, 237–258.

TROCONE, L., GALLI, G., SALVO, D., BARBARINO, A., and BONONO, L., 1977. Radioisotopic study of the adrenal glands using ^{131}I-19-iodocholesterol. *British Journal of Radiology, 50*, 340–349.

1978, *British Journal of Radiology*, *51*, 547–548 JULY 1978

Case reports

Renal involvement with non-Hodgkin's lymphoma: investigation of a recent case

By N. W. Garvie, M.A., M.R.C.P.,* J. M. G. Chu, B.Sc.(Med.), M.R.C.P., J. Nuttall, M.B., B.S., F.R.C.R., and V. R. McCready, M.Sc., M.R.C.P., F.R.C.R.

Isotope and Ultrasound Department and Department of Radiology, Royal Marsden Hospital, London

(*Received January, 1978*)

Renal involvement has been found at post-mortem in 35% of patients with lymphoma. It is more common with non-Hodgkin's lymphoma (Lalli, 1969). Only occasionally, however, is it the primary cause of death and the majority of patients lack urinary symptoms. Demonstration of renal involvement, which may have important therapeutic implications, may be enhanced by the use of non-radiological techniques. The following case is an illustration.

CASE REPORT

A 25-year-old Iranian woman presented with superior vena caval obstruction due to a large mediastinal mass, which was found to be a non-Hodgkin's lymphoma of diffuse type on biopsy. There was satisfactory response to radiotherapy, but she subsequently developed a right sided renal mass. This responded to chemotherapy, but recurred. Ultrasound scanning revealed small circular non-echogenic areas within both kidneys consistent with lymphomatous deposits (Fig. 1). Intravenous urography failed to show any abnormality at this time, but one month later revealed enlarged kidneys with extensive calyceal amputation, suggestive of focal deposits (Fig. 2). A gallium scan, which was performed to stage the lymphoma (Greenlaw *et al.*, 1974) also revealed renal involvement (Fig. 3).

The patient was given a further course of radiation and a follow-up ultrasound scan showed satisfactory regression of the renal lesions.

DISCUSSION

Renal involvement with lymphoma is probably more common than appreciated, particularly in non-Hodgkin's lymphoma. Knowledge of its presence

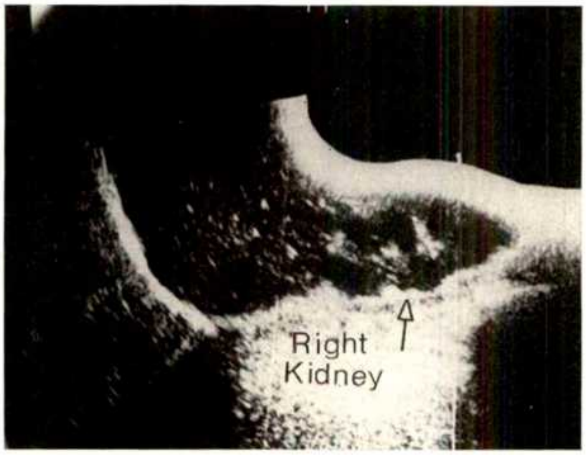


FIG. 1.

Sagittal section through liver and right kidney. Multiple spherical non-echogenic (dark) areas due to lymphomatous deposits.

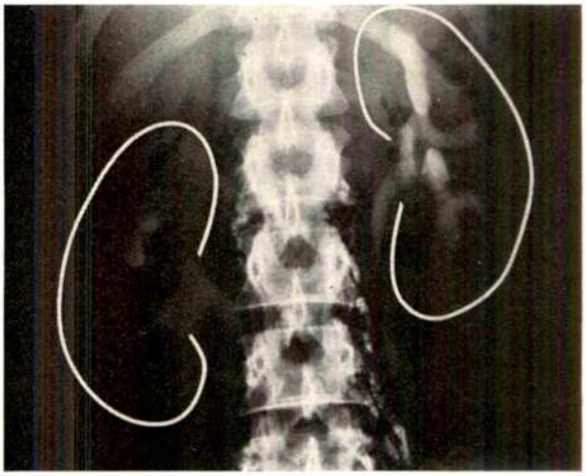


FIG. 2.

Intravenous pyelogram. Enlarged kidneys with extensive calyceal amputation.

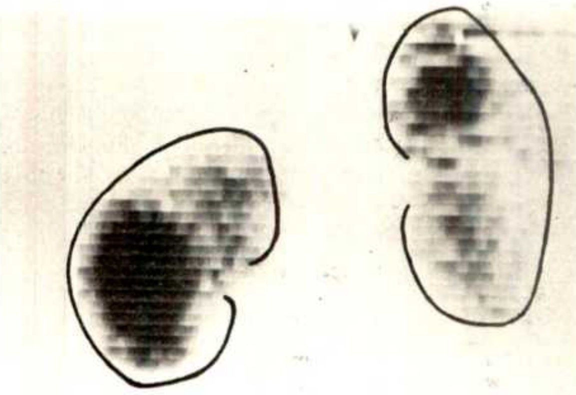


FIG. 3.

Gallium-67 scan. Renal outlines marked in.

---

*Present address: Wessex Regional Department of Nuclear Medicine, General Hospital, Southampton.

may contribute to effective management of the patient. Two varieties are recognized—diffuse infiltration or focal deposits, although both types may co-exist. It may be difficult to assess the presence of renal involvement on intravenous urography.

Ultrasound is able to resolve renal lesions above 0.5 cm in diameter. Focal lymphomatous deposits resemble multiple cysts (Filly *et al.*, 1976), but lack the bright border that cysts usually manifest. Gallium-67 as an isotope imaging agent may demonstrate renal involvement, but is limited by secretion into overlying large intestine. However this will be improved by adequate bowel cleansing (Levi *et al.*, 1975).

Ultrasound and isotope imaging are both non-invasive techniques and should be considered prior to arteriography or renal biopsy. We conclude that these methods have a role to play in the diagnosis of renal lymphoma.

REFERENCES

Lalli, A. F., 1969. Lymphoma of the urinary tract. *Radiology*, 93, 1051–1054.

Greenlaw, R. H., Weinstein, M. B., Brill, A. B., McBain, J. K., Murphy, L., and Kriseley, R. M., 1974. ^{67}Ga citrate imaging in untreated malignant lymphoma. *Journal of Nuclear Medicine*, *15*, 404–407.

Filly, R. A., Marglin, S., and Castellino, R. A., 1976. The ultrasonographic spectrum of abdominal and pelvic Hodgkin's disease and non-Hodgkin's lymphoma. *Cancer*, *38*, 2143–2148.

Levi, J. A., O'Connell, M. J., Linell, W., Sutherland, J. C., and Wiernik, P. H., 1975. Role of gallium citrate scanning in the management of non-Hodgkin's lymphoma. *Cancer*, *36*, 1690–1701.

Pleural cyst of the mediastinum

By D. L. Klein, M.D.

Department of Radiology, University of California School of Medicine, San Francisco, California, U.S.A.

(*Received October, 1977 and in revised form January, 1978*)

Pleural (mesothelial) cyst is an uncommon developmental anomaly of the parietal pleura (Clough and Beirne, 1955). It usually arises from the parietal pericardium, typically in the right cardiophrenic angle (Drash and Hyer, 1950). Less frequently, it is found on the surface of the diaphragm (Clough and Beirne, 1955; Freedman and Simon, 1936). Rarely does a pleural cyst arise from the parietal pleural covering of the upper mediastinum and paravertebral areas and present radiographically as a mediastinal mass (Jamplis *et al.*, 1963). Only two cases have been reported in which it arises from the posterior mediastinum (Jamplis *et al.*, 1963; Robbins, 1943). Pleural cysts are currently not included in the differential diagnosis tables for posterior mediastinal masses in standard reference texts (Fraser and Paré, 1970; Reeder and Felson, 1975).

Case Report

A 37-year-old woman was found to have a posterior mediastinal mass on routine chest film. She was entirely asymptomatic. She smoked half a pack of cigarettes per day. The results of physical examination and routine laboratory studies were entirely normal.

The P.A. chest film (Fig. 1A) demonstrated a well-circumscribed, round mass, 2 cm in diameter, just above the aortic knob at the level of the posterior 4th intercostal space. On the lateral film (Fig. 1B), the mass was posteriorly overlying the 4th and 5th thoracic vertebral bodies. No additional radiographic procedures were performed. The pre-operative diagnosis was a probable neurofibroma.

The patient underwent exploratory thoracotomy and was found to have a thin-walled, fluid-filled, pleural cyst in the left 4th intercostal space. The cyst was removed without difficulty, and the patient had an uneventful recovery.

Microscopically, the cyst wall demonstrated a single layer of mesothelial cells and a fibrous tissue stroma. The histologic diagnosis was pleural (mesothelial) cyst.

Discussion

Pleural cysts apparently occur because, embryologically, mesothelial lacunae (from which the pericardium and pleura are to be formed) fail to fuse (Drash and Hyer, 1950; Ochsner and Ochsner, 1966) They are thin-walled and usually contain a clear fluid. They are not known to have a malignant potential.

A pleural cyst never produces symptoms and is usually discovered on routine chest X-ray film. If it is at the right cardiophrenic angle, pleuropericardial cyst is the likely diagnosis, and surgery is frequently unnecessary. Pleural cysts otherwise occur on the diaphragmatic and mediastinal surfaces. Exploratory thoracotomy is necessary to rule out other lesions in these locations.

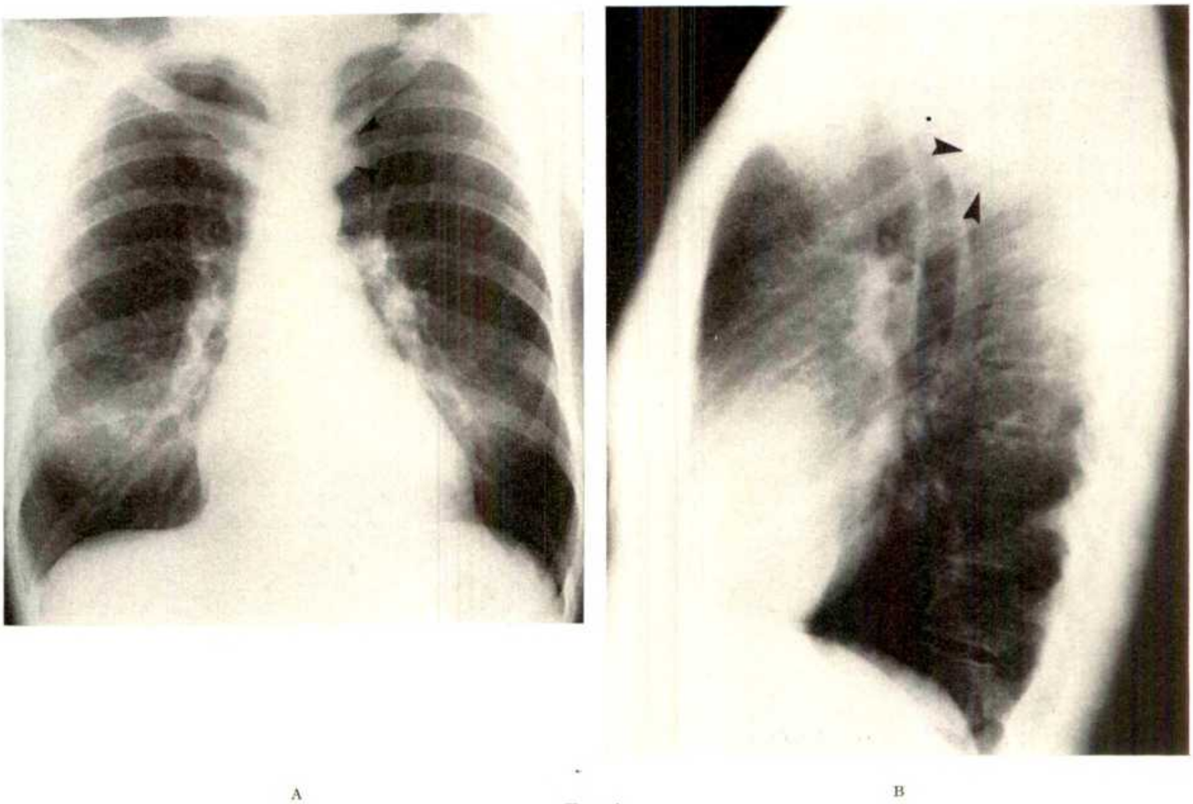


FIG. 1.

(A) P.A. chest film showing a sharply circumscribed, 2-cm mass (arrowheads) directly above the aortic knob on the left. (B) Lateral projection showing the mass (arrowheads) posteriorly overlying the vertebral bodies of T_4 and T_5.

REFERENCES

CLOUGH, D. M., and BEIRNE, M., 1955. Benign mesothelial cyst of the diaphragm. *Journal of Thoracic Surgery*, *29*, 212–216.

DRASH, E. C., and HYER, H. J., 1950. Mesothelial mediastinal cysts: pericardial celomic cysts of Lambert. *Journal of Thoracic Surgery*, *19*, 755–767.

FREEDMAN, E., and SIMON, M. A., 1936. Simple cyst of the pleura. Report of a case. *American Journal of Roentgenology*, *35*, 53–56.

FRASER, R. G., and PARÉ, J. A. P., 1970. *Diagnosis of Diseases of the Chest*. p. 1192. (W. B. Saunders, Philadelphia).

JAMPLIS, R. W., LILLINGTON, G. A., and MILLS, W., Jr. 1963. Pleural cysts simulating mediastinal tumours. *Journal of the American Medical Association*, *185*, 727–728.

OCHSNER, J. L., and OCHSNER, S. F., 1966. Congenital cysts of the mediastinum: 20-year experience with 42 cases. *Annals of Surgery*. *163*, 909–920.

REEDER, M. M., and FELSON, B., 1975. *Gamuts in Radiology*, (Audiovisual Radiography of Cincinnati, Inc., Cincinnati, Ohio), P. Gamut F–51.

ROBBINS, L. L., 1943. The roentgenologic appearance of "bronchogenic" cysts. *American Journal of Roentgenology*, *50*, 321–333.

Book review

An atlas of cardiology: electrocardiograms and chest X-rays. By Neville Conway Illus., 1977 (Wolfe Medical Publications Limited), £12·00.

This book consists of some 450 electrocardiograms and 300 chest X rays which illustrate all the common, and some of the less common, abnormalities seen in clinical practice. It is very well produced and the illustrations are of a very high standard. There will be few, other than experienced cardiologists and radiologists, who will not profit from browsing through it. It is essentially practical and discussion of the theoretical basis of electrocardiography is deliberately kept to a minimum. The index is very comprehensive and includes references to specific electrocardiographic and radiographic features as well as to disease entities; it thus allows the atlas to be used as a "bench book" for ready reference as is the author's intention. It can be strongly recommended.

P. R. FLEMING.

1978, *British Journal of Radiology*, *51*, 550–551

Short communications

Measurements of the OER and RBE for neutrons generated by 70 MeV protons on lithium

By M. Guichard, B.Sc., J. Gueulette, B.Sc., G. Laublin, B.Sc., A. Wambersie, M.D., Ph.D., and E. P. Malaise, M.D., Ph.D.

Institut de Radiobiologie Clinique, Institut Gustave-Roussy, 94800 Villejuif, France

(*Received January, 1978*)

A study of physical and biological properties of neutrons generated with deuterons in the range 16 to 50 MeV shows that, as energy increases, there is an improvement of the depth dose distribution without an appreciable change in the oxygen enhancement ratio (OER). On the other hand, one observes a decrease in the relative biological effectiveness (RBE). In order to improve the distribution of the dose further, it appears desirable to raise the energy of the neutrons to a level greater than that of neutrons generated by 50 MeV deuterons on Be. The biological properties of neutrons at such energies are not well known. Using *vicia faba*, Harrison *et al.* (1975; 1976) found that the OER decreased on the average from 1.8 to 1.2 with neutrons whose maximum energy increased from 35 to 101 MeV. The reduction in the OER might be due to an increase in the level of spallation products. On the other hand, using *vicia faba*, Hall (1976) and Hall *et al.* (1977a, b) found that the OER increased from 1.6 to 1.7 when the maximum energy of the neutrons increased from 50 MeV to either 66 or 80 MeV. For mammalian cells, Hall using V 79 cells found an OER of 1.5 for neutrons of maximum energy 35 MeV and an OER of 1.7 for neutrons of maximum energy 66 or 80 MeV.

Confronted with these fragmentary and somewhat contradictory results, new experiments appeared desirable using neutrons of higher energy. We had the possibility of working with two energies of neutron: 50 MeV $d^+ \rightarrow Be$ (Guichard *et al.*, 1978) and 70 MeV $p^+ \rightarrow Li$ produced by the "Cyclone" cyclotron at Louvain-la-Neuve (Belgium). We have studied both the OER and the RBE of these two types of radiation for V 79 cells. We irradiated the cells in suspension in glass ampoules using a method described elsewhere (Guichard *et al.*, 1978). During the irradiation, the ampoules were placed in a plexiglass (Perspex) box. The average thickness of the plexiglass traversed by the neutrons before reaching the ampoule was 2.2 cm. For each experiment, a number of control ampoules were irradiated with γ rays from ^{60}Co, not only in order to measure the OER but also the gain factor (ratio between OER with ^{60}Co γ rays and OER with neutrons).

The gain factor (GF) obtained with the 70 MeV $p^+ \rightarrow Li$ neutrons (Fig. 1, Table I) is greater than that found previously with the 50 MeV $d^+ \rightarrow Be$ neutrons (2.2 and 1.9 respectively). Moreover, the OER obtained previously with the 50 MeV d^+Be neutrons was a little greater than that obtained now with the 70 MeV p^+Li neutrons (2.0 and 1.9 respectively). On the other hand, the RBE measured at a survival level of 10^{-1} was 1.4, while we found 2.1 for the less energetic 50 MeV d^+Be neutrons (Guichard *et al.*, 1978). In this energy range, *i.e.* between maximum energies of 50 and 70 MeV, it seems evident that the variations in OER are small. This is the conclusion of experiments carried out with mammalian cells both by us and by Hall (1976) and Hall *et al.* (1977a).

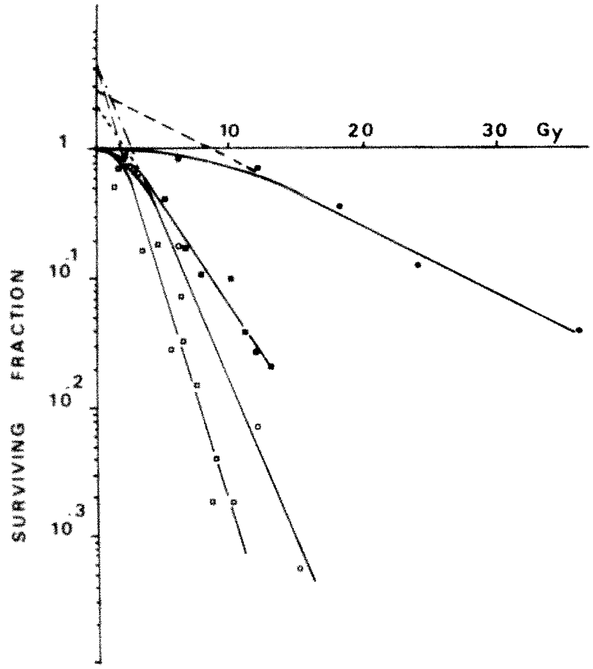


FIG. 1.

Survival curves for cells irradiated under aerated and hypoxic conditions with 70 MeV $d^+ \rightarrow Li$ neutrons and ^{60}Co γ rays.

□——□—70 MeV $p^+ \rightarrow Li$ neutrons air
■——■—70 MeV $p^+ \rightarrow Li$ neutrons hypoxia
○——○—^{60}Co γ rays air
●——●—^{60}Co γ rays hypoxia

TABLE I

SURVIVAL CURVE PARAMETERS FOR ^{60}Co γ RAYS AND 70 MEV $p^+ \rightarrow Li$ NEUTRONS. VALUES OF OER, GF AND RBE

		n	D_0	OER level 10^{-1}	GF	RBE level 10^{-1}
^{60}Co γ rays	Air N_2	4.8 2.9	174 824	4.1		1
70 MeV $p^+ \rightarrow Li$ neutrons	Air N_2	4.2 2.2	126 281	1.9	2.2	1.4

This investigation was supported by contract BC 1027 from the Commissariat à l'énergie atomique and by contract No. 76.7.1686.01 from the DGRST.

This suggests that 70 MeV $p^+ \to$ Li neutrons could be useful in radiotherapy since the gain factor remains elevated and the depth dose distribution is good. However, it seems evident that the RBE is substantially reduced. If one should consider the RBE as a gain factor in radiotherapy, as for example does Barendsen (1974), this could reduce interest in increasing the neutron energy from 50 to 70 MeV.

ACKNOWLEDGMENTS

We wish to thank Mr. J. P. Meulders (Unité de Radiophysique Nucléaire at Louvain-la-Neuve), Mr. M. Winant and Mrs. M. Octave-Prignot (Unité de Radiothérapie in Louvain) who performed the dosimetry.

REFERENCES

BARENDSEN, G. W., 1974. Characteristics of tumour responses to different radiations and the relative biological effectiveness of fast neutrons. *European Journal of Cancer*, *10*, 269–274.

HALL, E. J., 1976. Intercomparative biological dosimetry. Cells *in vitro*. In *Particle radiation therapy*. Proceedings of an international workshop, eds. V. P. Smith, pp. 187–202 (American College of Radiology, Philadelphia, Pennsylvania, 19107).

HALL, E. J., GEARD, C., COFFEY, R. J., and HALL, B. E., 1977a. Measurements of the oxygen enhancement ratio for high energy neutrons at the Fermilab. *International Journal of Radiation Oncology, Biology and Physics*, *2*, 105–110.

HALL, E. J., GEARD, C. R., POVLAS, S., and ASTOR, M., 1977b. The oxygen enhancement ratio for high energy neutrons. *British Journal of Radiology*, *50*, 679–680.

HARRISON, G. H., KUBICZEK, E. B., and ROBINSON, J. E., 1975. OER of neutrons from 80 MeV deuterons on beryllium. *British Journal of Radiology*, *48*, 409–410.

1976. OER reduction with high energy neutrons. *British Journal of Radiology*, *49*, 733.

GUICHARD, M., GUEULETTE, J., LAUBLIN, G., WAMBERSIE, A., and MALAISE, E. P., 1978. The comparative response of human fibroblast EMT 6 and V 79 cells to 50 MeV neutrons. *International Journal of Radiation Oncology, Biology and Physics* (in press).

Radioprotection of mammalian cells by procaine

By T. M. Yau, Ph.D. and S. C. Kim, M.S.

Division of Radiation Biology, Department of Radiology, Case Western Reserve University, Cleveland, Ohio 44106, U.S.A.

(*Received December, 1977*)

The cellular membrane has been recognized for some time as an important target for radiation injury (Myers, 1970; Alper, 1971). In addition to this, it is also believed to play an important role in repair processes, thus influencing the ultimate survival of the irradiated cells. In an attempt to elucidate these mechanisms further, we have examined the ability of certain "membrane-active" compounds to modify the radiation response of mammalian cells under various experimental conditions. In this report we present the radioprotective effect afforded by a local anaesthetic, procaine hydrochloride (PH), on L5178Y, a murine leukaemic cell line.

Asynchronous L5178Y cells were grown in Fischer's Medium plus 10% horse serum. Cultures were harvested by centrifugation and resuspended in serum-free medium to a final concentration of 2×10^5 cells/ml. Cells were irradiated at room temperature with a Picker 250 kV X-ray generator at a dose rate of 60 rad/min. An appropriate amount of 1 M PH solution, made up in saline, was added just prior to X-irradiation. Immediately after irradiation, cells were resuspended in fresh medium to remove the drug. The survival of cells was monitored by dye exclusion, growth extrapolation, or colony formation.

The percentage of L5178Y (subline N) cells excluding trypan blue as a function of time after 400 rad X-irradiation in the absence and presence of PH (10 mM) is shown in Table I. No alteration in dye exclusion is discernible immediately after irradiation. However, at two and three days post-irradiation a significantly higher proportion of procaine-treated cells still maintain the ability to exclude the vital stain. Since dye exclusion should only be considered as an indicator of cell membrane integrity rather than cell viability, the proliferative capacity of irradiated cultures was also assessed. In Fig. 1, the cell growth kinetics of L5178Y cells (subline R_1) irradiated with 200, 400 and 600 rad of X rays in the absence and presence of PH (2 mM) is presented. If one assumes that the deviation from exponential growth is associated with radiation damage, then the protective effect afforded by PH becomes apparent at the initial portion of the growth curves. Extrapolation of the exponential portion of the growth curves back to the time of irradiation also indicates that the initial surviving fraction of cells irradiated in the presence of PH is invariably greater with all the doses employed. Finally, radioprotection by PH in cells was ascertained by the ability of irradiated cells to form colonies in soft agar. For this latter end point, the dose modifying factor for PH is approximately 1.4 at the 10% survival level (Fig. 2).

The specific mechanisms whereby PH protects mammalian cells from radiation damage is not known at present. Since PH belongs to a general class of compounds which manifest their pharmacological effects through interaction with membranes (Seeman, 1972), it appears reasonable to suggest that the observed radioprotective capacity may be related to their ability to interact specifically with the cellular membrane. It has been reported from another laboratory that PH sensitizes cells under hypoxic conditions (Shenoy, *et al.*, 1974; George *et al.*, 1975). Although a number of different cell types were studied, including some mammalian cells, no rigorous survival test such as colony formation was performed except for *E. coli*. In any event, the authors failed to observe any radioprotective effect of PH in air. We are

TABLE I

EFFECT OF PROCAINE HYDROCHLORIDE ON DYE EXCLUSION IN X-IRRADIATED L5178Y CELLS

Days post X irradiation	Cells irradiated without procaine	Cells irradiated with 10 mM procaine
0	95%	95%
2	58%	74%
3	15%	32%
6	90%	90%

Aliquots of cell suspension were incubated with 0.4% trypan blue and counted under the microscope with the aid of a haemocytometer after incubation at room temperature for 10 min.

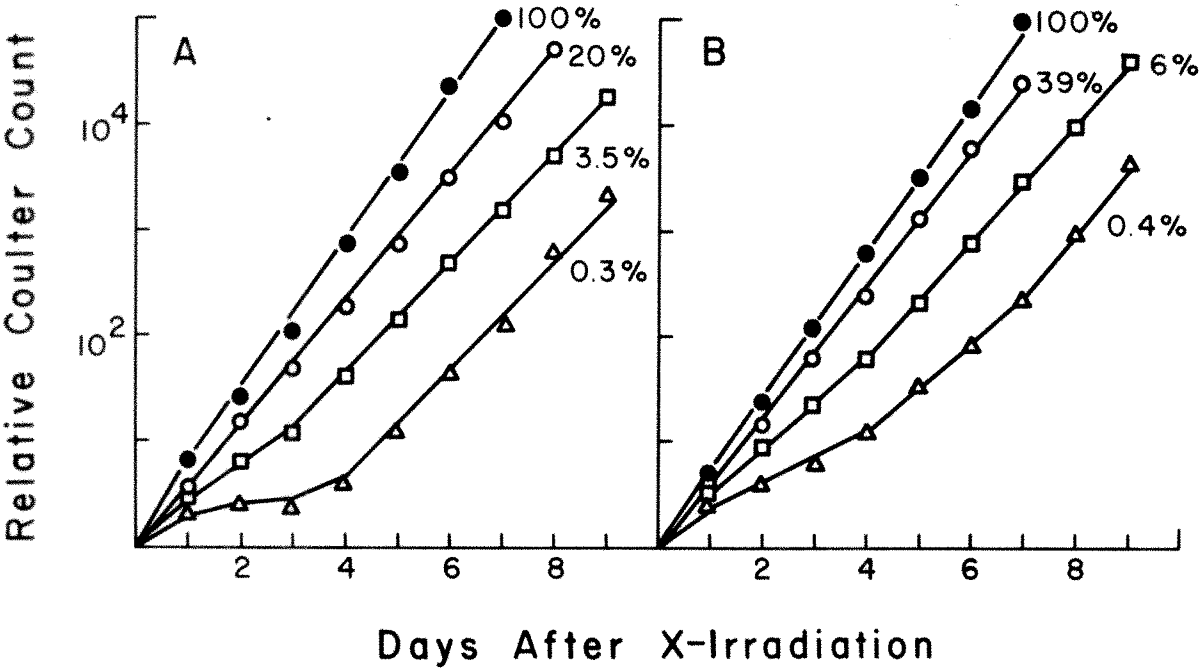


FIG. 1.

Growth kinetics of L5178Y cells irradiated in the absence (A) and presence (B) of 2 mM PH.

●——● 0 rad
○——○ 200 rad
□——□ 400 rad
△——△ 600 rad

Percentages denote the initial surviving fraction estimated by back-extrapolation.

currently engaged in further experimentation to test if PH and related compounds can protect oxic and sensitize hypoxic cells.

This project has been partly supported by Research Grant CA-15901 from the National Cancer Institute, DHEW, T.M.Y. is the Harry H. Pinney Scholar for Cancer Research at Case Western Reserve University.

REFERENCES

ALPER, T., 1971. Cell death and its modification: the roles of primary lesions in membranes and DNA. In *Biophysical aspects of radiation quality*, p. 171 (IAEA, Vienna).

GEORGE, K. C., SHENOY, M. A., JOSHI, D. S., BHATT, B. Y., SINGH, B. B., and GOPAL-AYENGAR, A. R., 1975. Modification of radiation effects on cells by membrane binding agents—Procaine HCL. *British Journal of Radiology*, *48*, 611–614.

MYERS, D. K., 1970. Some aspects of radiation effects on cell membranes. *Advances in Biological and Medical Physics*, *13*, 219–234.

SEEMAN, P., 1972. The membrane actions of anaesthetics and tranquilizers. *Pharmacological Reviews*, *24*, 583–655.

SHENOY, M. A., SINGH, B. B., and GOPAL-AYENGAR, A. R., 1974. Enhancement of radiation lethality of *E. coli B/r* by procaine hydrochloride. *Nature*, *248*, 415–416.

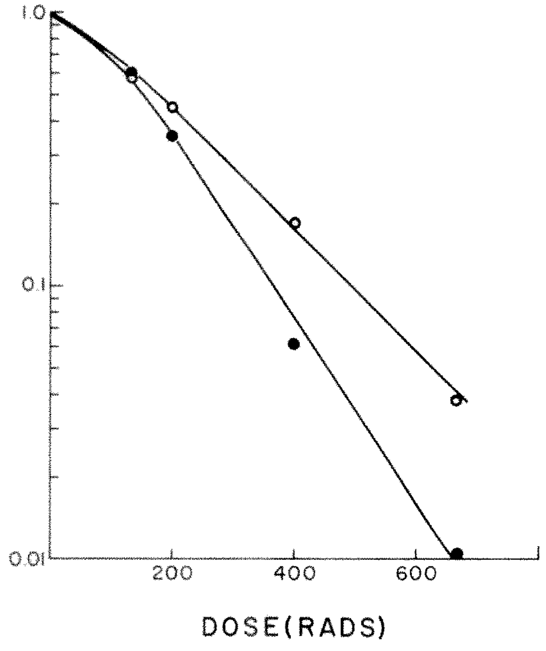


FIG. 2.

Modification of radiation response of L5178Y cells by PH as assessed by colony formation in soft agar.

●——● control
○——○ 10 mM PH

1978, *British Journal of Radiology*, *51*, 553–556

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Thyroid irradiation and the new ICRP dose limits

THE EDITOR—SIR,

The application of the ICRP (1977) recommendations to irradiation of the thyroid by medically used radionuclides raises some questions which should be thoroughly discussed before the new system of dose limitation is incorporated into local rules or national codes of practice. In particular, the following topics need to be raised:

(a) The size of the annual dose-equivalent limits for medically used radionuclides.

(b) The level and acceptability of the associated risks, which are probably higher than would be suggested by the relevant ICRP weighting factor.

(c) The relationship of these levels of risk to other comments in the ICRP recommendations.

(d) The advisability or otherwise of using a stricter system of dose limitation and medical surveillance to limit the consequences of thyroid irradiation.

The size of the dose equivalent limit.

The new ICRP recommendations have moved from the formerly used practice of specifying the maximum permissible dose to particular organs. Instead, the total risk associated with a whole body dose of five rem/year is regarded as the maximum permissible. To derive the dose allowed to a particular organ, weighting factors (w) have been defined which are related to the proportion of the total risk associated with the organ in question. The weighting factor for the thyroid is 0.03 and that for the rest of the body is 0.97. In circumstances where the thyroid is irradiated by a radionuclide the dose-equivalent limits for the gland (H_t) and the rest of the body (H_{rb}) are related as follows:

$$0.03H_t + 0.97\,H_{rb} = 5\text{ rem.}$$

This is the relevant form of the equation in paragraph 104 of ICRP (1977), assuming the rest of the body is uniformly irradiated. If we assume that the ratio of the dose to the thyroid to that to the rest of the body for a given radionuclide is k, we can solve the above equation to give the maximum permissible dose-equivalent to the thyroid as

$$H_t = \frac{5}{0.03+0.97/\text{k}}\text{ rem} \quad . \; . \; . \; . \quad (1)$$

Approximate values for k calculated from data published by the MIRD Committee (MIRD, 1975; 1976) are listed in Table I for commonly used radionuclides that are likely to lead to significant thyroid exposure. Substituting these values in equation (1) gives the maximum permissible dose-equivalent to the gland for the various radionuclides. These are also listed in Table I, and in most cases, except $^{99}\text{Tc}^{\text{m}}$, are in region of 150 rem. However, all of the ICRP dose-equivalent limits are subject to the constraint that they should not be greater than 50 rem, a level which is set primarily with the object of preventing non-stochastic effects. Therefore, it is important to note that in medical work the three most frequently used radioisotopes of iodine will have limits on intake which are set by the 50 rem value for non-stochastic effects rather than by the weighting factors and 5 rem whole body limit used to derive values for other tissues.

A 50 rem limit on thyroid irradiation represents a substantial increase over previous values applied to this gland and a significant change in the trend to reduce the dose allowed to it. In the differentiation of dose limits allowed to various organs and tissues during the late 1940's and early 1950's the thyroid was assigned a maximum permissible dose of 30 rad /year (Taylor, 1971) because it was thought to be radioresistant. This practice persisted for some time (ICRP 1966, IAEA 1962), and the value has been used in some recent directives (Euratom, 1976; HMSO, 1972; IAEA, 1973; ICRP, 1976). Nevertheless, since the late 1960's some codes of practice and recommendations reduced the dose-equivalent allowed to the thyroid to 15 rem/year (Taylor, 1971; NCRP, 1971), because of the mounting evidence for radiation-induced thyroid neoplasia. The size of the dose-equivalent limit allowed by the ICRP (1977) recommendations represents a reversal of this trend. It arises directly from the use of the system of weighting factors in a situation where the differential between the dose to the whole body and that to the organ in question is very large. This indicates a potential weakness which may lie in the system itself or in the numerical values of the weighting factors used in it.

TABLE I

RATIO OF THYROID TO WHOLE BODY DOSE, AND MAXIMUM PERMISSIBLE DOSE-EQUIVALENT TO THE THYROID CALCULATED FROM ICRP (1977) WEIGHTING FACTORS

Uptake	RatioThyroid/Whole Body Dose (k)			
%	^{125}I	^{131}I	^{132}I	^{99}Tc$^{\text{m}}$*
15	1552	1702	74	10
25	1612	1831	118	
	Maximum dose-equivalent to thyroid based on weighting factors (rem)			
15	163	164	116	39
25	163	164	131	

*The uptake values do not apply to $^{99}\text{Tc}^{\text{m}}$.

The level of risk associated with the dose-equivalent limit for the thyroid

The new ICRP recommendations present the risk figures associated with a particular dose-equivalent in a fashion that takes account of the life-time risk of inducing malignant disease after exposure and the frequency of fatalities for those who acquire the disease. Taking both of these factors into account the value quoted for the thyroid is 5×10^{-6}/rem for the probability of a fatal cancer. This is qualified by reference to the fact that thyroid cancers are frequently not fatal and hence the risk of a cancer is considerably greater than that of a fatal one. Therefore to assess the magnitude of the risk of *malignancy* or other *neoplastic development*, as opposed to fatality, requires a more detailed study.

Much information is now available on the carcinogenic action of radiation in the thyroid that was not to hand when it was originally assigned a large maximum permissible dose (Taylor, 1971). The epidemiological evidence linking neoplastic development in the gland with irradiation is indisputable, particularly in children (BEIR, 1972). It is based on a wide variety of experience ranging from the aftermath of nuclear explosions (Conard, 1975) through therapeutic medical use (Duffy and Fitzgerald, 1950; Saenger and Keriakes, 1971) to occasional reports after diagnostic medical use (Malone, 1975). Furthermore the available data

TABLE II

RISK OF BENIGN AND MALIGNANT NEOPLASIA IN THYROID AFTER IRRADIATION

Risk (per 10^6 man-rem per year)		Source
Malignant Neoplasia	Benign Neoplasia	
1.6–9.3	75% of those receiving 1000 rad	BEIR, 1972
3.4*	49+	Conard, 1975
†Approx 10	—	Modan *et al.*, 1974, 1977.

*Mean values from 10 groups cited by Conard (1975)
†Approximate value estimated from data in Modan (1977).

demonstrate that radiation-induced thyroid neoplasia occur at doses as low as 6.5 rad (Modan, *et al.*, 1974).

Data on induction of cancer in the thyroid were critically reviewed by the BEIR Committee (1972) and have been summarized more recently by Conard (1975) The main data in addition to the above are those of Modan *et al.* (1974; 1977) which have also been subject to some analytical comment (Pochin, 1976). The risk estimates for malignant and benign neoplastic developments from these reports are summarized in Table II. For calculation purposes a value of 3×10^{-6} per man-rad per year will be taken for induction of malignancies. The rate at which benign adenomas occur is greater but more uncertain and appears to range from twice to fifty times the rate for carcinomas. However, for calculation purposes the data from Conard (1975) in Table II and work in animals (Doniach, 1958) indicate that it is not unreasonable to use a value of 10. The dose rates that prevailed in the populations on which these figures are based were higher than those that would give rise to 50 rem acquired at a uniform rate over a year.

The epidemiological investigations cited above have been carried out to a large extent in children, and are supported by extensive experimental work in animals. These investigations confirm the sensitivity of the thyroid to low radiation doses (Moore and Colvin, 1968), and clearly identify irradiation as a co-factor in the tumour-induction process (Doniach, 1971; Hempleman, 1969; Lindsay, 1969; Walinder, 1972). This process requires that some time after irradiation the thyroid be subjected to a stress leading to cell division, for example by TSH or other humeral factors with a similar effect on the gland. The fact that the gland comes under such pressures naturally during adolescence is thought to explain the high tumour incidence in young adults whose thyroids were irradiated while they were children. It is also likely that similar mechanisms operate in adults whose thyroid is subject to hormonal pressures arising naturally, for example from pregnancy, through disease or through dietary factors (Conard, 1975; Hempleman, 1969; Doniach, *et al.*, 1966). Therefore, it appears that particular groups of adults, such as those with an abnormal thyroid status, may be highly susceptible to radiation-induced thyroid neoplasia. Consequently, while these risk estimates are for the greater part based on the results of investigations of populations irradiated during childhood, they should not be ignored for the adult population, and with respect to special subgroups of the adult population may in fact be as representative of the true risk as they are for children. This is supported by the fact that radiation-induced neoplasia have been noted in adult populations in studies of both animals and man (Conard, 1975; Walinder, 1972a, b; Doniach *et al.*, 1966).

TABLE III

PERCENTAGE CHANCE OF BENIGN OR MALIGNANT NEOPLASIA OR FATALITY AFTER RECEIVING VARIOUS DOSES TO THE THYROID FOR ONE YEAR OR EACH YEAR FOR 40 YEARS. THE MEAN FOLLOW-UP PERIOD ASSUMED IN EACH CASE IS 30 YEARS.

One dose only (rem)	Percentage Chance		
	Malignant	Benign	Fatal (ICRP, 1977)
150	1.35	13·5	0·075
50	0·45	4·5	0.025
15	0.135	1.35	0.0075
5	0.045	0.45	0.0025
Dose each year for 40 years (rem)	Percentage Chance		
	Malignant	Benign	Fatal (ICRP, 1977)
150	54.0	540	3.0
50	18.0	180	1.0
15	5.4	54	0.3
5	1.8	18	0.1

Table III lists the consequences of these risk estimates for workers receiving various annual doses during a 40-year working life with an average follow-up period of 30 years. These figures suggest that the risk of malignancy for a worker receiving the maximum permissible dose (50 rem) would be 18% and that of a benign adenoma would be 180%. The adenoma risk appears somewhat high compared with Pochin's (1964) estimate of 0.5 to 1% of the adult population per 100 rad. However it is in keeping with an estimate of "75% of those receiving 1000 rad". Again it must be emphasized that these figures are derived from populations irradiated during childhood, and hence for the general adult population represent worst possible estimates, but for subgroups of the adult population they may be quite appropriate.

While the risks quoted above do not imply a fatal outcome they are relatively high, and it is doubtful if they would be knowingly accepted by many radiation workers. Furthermore, even in the absence of malignant disease a radiation worker who developed a benign neoplasim would almost inevitably face the prospect of extensive thyroidal investigations, some involving further radiation dosage. This might be followed by exploratory surgery, lobectomy and the inconvenience of the subsequent follow-up. Therefore there is a substantial non-fatal burden of harm associated with thyroid irradiation that is in a crude sense quantifiable.

Relationship of levels of risk with other ICRP comments.

The advantage of the ICRP (1977) recommendation for dose limitation, based on weighting factors and the whole body dose equivalent limit of five rems, is that it produces a conceptually simple, uniform and consistent system of dose limitation. However, as demonstrated above, the system is not applicable to the thyroid when it is irradiated by many medically used radionuclides. Instead the arbitrary limit of 50 rem primarily designed to prevent non-stochastic effects must be used. This limit may have been selected without reference to the peculiar radiobiological properties of the thyroid that lead to a very high proportion of non-fatal harm. Therefore there is a good case for selecting another arbitrary but lower maximum permissible dose-equivalent for the thyroid. For example a reduction to 5 rem/year would give the risk figures indicated in Table III, which appear more acceptable. The same considerations apply to the maximum permissible dose values recommended for members of the general public.

This problem may also be approached from the point of view of non-stochastic effects such as eye damage, which the commission aims to prevent. While induction of thyroid nodules does not fit within the strict definition of non-stochastic effects, there are certain similarities. These arise, for example, from the liklihood of surgical intervention to correct radiation-induced damage, or the possibility of becoming dependent on artificial aids such as hormone substitutes in the case of the thyroid, or spectacles in the case of the eye. Therefore a case could be made for re-classifying benign thyroid neoplasia with non-stochastic effects. This could lead to a special dose equivalent limit for the gland such as 5 rem/year just as the special 30 rem/year limit is applied to the eyes.

Advisability of changing the dose limit for the thyroid.

The above discussion demonstrates that the maximum dose-equivalent of 50 rem allowed to the thyroid may be too large. The level of risk of non-fatal neoplasia would probably not willingly be accepted by many radiation workers, particularly as in practice there is no real difficulty in keeping the thyroid dose of medical radiation workers below, for example, five rem/year (ICRP, 1971; Fiege *et al.*, 1971; Birchall, 1977). To achieve the level of 50 rem/year would require a continuous radioiodine content in the gland that approaches the levels present during diagnostic investigations (de Groot and Stanbury, 1975). In view of these considerations it is desirable to consider additional proposals to limit irradiation of the thyroid, or the risk consequent on such irradiation, or both. Examples of proposals that would be effective in this regard are:

(a) The maximum permissible dose to the thyroid from radionuclides should be limited to five rem per year until a formal scheme of integrating the burden of harm from non-fatal hazards into the system of dose limitation becomes available.

(b) Workers engaged in using radionuclides of iodine, or other radionuclides with similar dosimetric properties, should be medically screened to determine if they are in a group likely to be at special risk of developing thyroid neoplasia. The screening procedure might involve determination of thyroid status through normal biochemical indicators (T_3, T_4, etc.) and the levels of hormones such as TSH which act on the gland. If an abnormal thyroid status or other risk factor is identified the worker should be removed from tasks involving a high risk of ingestion of radioiodine and have the dose allowed to his/her gland reduced to that for a member of the general public.

Limitations on thyroid exposure of this kind might usefully be incorporated into local rules pending a clarification of the issues raised by the non-fatal hazards of thyroid irradiation. These proposals might also be usefully considered in relation to the revised control measures for radiation being formulated in EEC countries to meet the requirements of the Euratom Directive (1976) which limits thyroid exposure to 30 rem/year.

Yours, etc.,
J. F. MALONE.

College of Technology,
Kevin Street,
Dublin 8.
and Meath Hospital,
Heytesbury Street,
Dublin 8.

REFERENCES

BEIR, 1972. In *The Effects on Populations of Exposure to low levels of Ionizing Radiation*, pp. 120–124 (National Academy of Sciences—National Research Council, Washington).

BIRCHALL, I., 1977. Problems with iodine-125 iodination. *Radiological Protection Bulletin (NRPB)*, *18*, 19–21.

CONARD, R. A., 1975. In *A Twenty year review of Medical findings in a Marshallese Population accidentally exposed to radioactive fallout.* Brookhaven National Laboratory BNL 50424, pp. 50–62 National Technical Information Service, Springfield, USA).

DE GROOT, L., and STANBURY, J., 1975. In *The Thyroid and its Deseases*, p. 219 (Wiley, London and New York).

DONIACH, I., 1958. Experimental induction of tumours of the thyroid by irradiation. *British Medical Bulletin*, *14*, 181–183.

1971. Radiation Biology. In *The Thyroid.* S. C. Werner and S. H. Ingbar (eds.), pp. 185–192.

DONIACH, I., EADIE, D. G. A., and HOPE-STONE, H. F., 1966. The development of a multiple thyroid adenomata in primary hyperthyroidism in previously irradiated thyroid glands. *British Journal of Surgery*, *53*, 681–685.

DUFFY, B. J., and FITZGERALD, P. J., 1950. Cancer of the thyroid in children—a report of 28 cases. *Journal of Clinical Endocrinology and Metabolism*, *10*, 1296–1308.

EURATOM, 1976. Council Directive of 1st June, 1976. *Official Journal of the European Communities*, *19*, 1–44.

FIEGE, Y., GAVRON, A., LUBIN, E., LEWITUS, Z., BEN-PORATH, M., GROSS, J., and LOEWINGER, E., 1971. Local energy deposition in thyroid cells due to the incorporation of ^{125}I. In *Biophysical Aspects of Radiation Quality*, pp. 383–404 (International Atomic Energy Agency, Vienna).

HEMPLEMAN, L. H., 1969. Radiation exposure and thyroid cancer in man. In *Thyroid Cancer*, C. Hedinger (ed.), pp.103–111 (Springer-Verlag, Berlin).

HMSO, 1972. *Code of Practice for the Protection of Persons against Ionizing Radiation arising from Medical and Dental Use*, pp. 78–81 (Her Majesty's Stationery Office, London).

IAEA, 1962. *Safe Handling of Radioisotopes*, pp. 67–79 (International Atomic Energy Agency, Vienna).

1973. *Radiation Protection Procedures*, pp. 40–45 (International Atomic Energy Agency, Safety Series No. 38, Vienna).

ICRP, 1966. Recommendations of the ICRP Publication 9, pp.10–14 (Pergamon Press, Oxford).

1971. *The Assessment of Internal Contamination Resulting from Recurrent or Prolonged uptakes*, pp. 12–33 (Pergamon Press, Oxford).

1976. *Recommendations of the International Commission on Radiological Protection, Publications 15 and 21*, p.34 (Pergamon Press, Oxford).

1977. *Recommendations of the International Commission on Radiological Protection, Annals of the ICRP*, Publication 26, 1–50.

LINDSAY, S., 1969. Ionizing radiation and experimental thyroid cancer—a review. In *Thyroid Cancer.* C. Hedinger (ed.), pp. 161–169 (Springer-Verlag, Berlin).

MALONE, J. F., 1975. The radiobiology of the thyroid. *Current Topics in Radiation Research*, *10*, 263–368.

MIRD, 1975. Summary of current radiation dose estimates to humans from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I, ^{132}I as sodium iodide. *Journal of Nuclear Medicine*, *16*, 857–860.

1976. Summary of current radiation dose estimates to normal humans from ^{99}Tc^{m} as sodium pertechnetate. *Journal of Nuclear Medicine*, *17*, 74–77.

MODAN, B., BAIDATZ, D., MART, H., STEINITZ, R., and LEVIN, S. G., 1974. Radiation induced head and neck tumours, *Lancet*, *i*, 277–279.

MODAN, B., RON, E., and WERNER, A., 1977. Head and neck tumours and impaired mental function following scalp irradiation. In *Proceedings of the 4th International Congress of IRPA*, pp. 723–725 (IRPA, Paris).

MOORE, W. P., and COLVIN, M., 1968. Chromosomal changes in the Chinese hamster thyroid following X-irradiation *in vivo*. *International Journal of Radiation Biology*, *14*, 161–167.

NCRP, 1971. *Basic Radiation Protection Criteria*, pp. 37, 76 and 92 (National Council on Radiation Protection, Report No. 39, Washington).

POCHIN, E. E., 1964. Radiation exposure from the use of radioiodine in thyroid disease. *Proceedings of the Royal Society of Medicine*, *57*, 564–565.

1976. Radiology now. Malignancies following low radiation exposures in man. *British Journal of Radiology*, *49*, 577–579.

SAENGER, E. L., and KEREIAKES, J. G., 1971. The safe tracer dose in medical investigation. *Progress in Atomic Medicine*, *3*, 139–165.

TAYLOR, L. S., 1971. *Radiation Protection Standards*, pp. 18, 26–32, 97 (Butterworths, London).

WALINDER, G., 1972a. Late effects of irradiation on the thyroid gland in mice. *Acta Radiologica, Therapy Physics Biology*, *11*, 433–451.

1972b. In *Radiation Effects on the Thyroid Glands of CBA mice* (Thesis, Stockholm).

Examination of small bowel by double contrast technique

THE EDITOR—SIR,

It is sad to reflect upon the failure of our colleagues to recognise the work of British radiology in the proceedings of the joint radiological meeting of the Institute and the Royal College in Leeds (*B.J.R.*, Feb. 1978, Vol. 51, No. 602, p.147).

Dr. Noakes, describing an alternative method of examination of the small bowel by a double contrast technique, refers to Sellink, 1976 and Fleckenstein and Pedersen, 1975, but makes no mention of the double contrast technique described some 16 years previously by Scott-Harden (1960, Scott-Harden *et al.*, 1961). Nor indeed does he give credit to the originators of the modification using 0.5% Prepacol as the flushing fluid. This modification was advocated by Trickey, *et al.* (1963).

Yours, etc.,
T. G. GIRDWOOD.

Department of Radiology,
Cumberland Infirmary,
Carlisle CA2 7HY.

REFERENCES

FLECKSTEIN, P., and PEDERSEN, G., 1975. The value of the duodenal intubation method (Sellink modification) for the radiological visualisation of the small bowel. *Scandinavian Journal of Gastro Enterology*, *10*, 423–425.

SCOTT-HARDEN, W. G. 1960. *Modern Trends in Diagnostic Radiology* (*3rd series*), ed. J. W. McLaren. p. 84 (Butterworth, London).

SCOTT-HARDEN, W. G., HAMILTON, H. A. R., and MCCALL-SMTIH, S., 1961. Radiological investigation of the small intestine. *GUT*, *2*, 316–322.

SELLINK, J. L., 1976. *Radiological Atlas of Common Diseases of the Small bowel* (H. E. Stenfert Kroese, B. V., Pieterskrerkof 38, P.O. Box 33, Leyden, The Netherlands).

TRICKEY, S. E., HALLS, J., and HODSON, C. J., 1963. A further development of the small bowel enema. *Proceedings of the Royal Society of Medicine*, *56*, 1070–1073.

The use of sodium chloride injection B.P. in the preparation of radiopharmaceuticals

THE EDITOR—SIR,

In recent months, problems have arisen with the red cell labelling procedure used in our department. On four separate occasions, ^{51}Cr sodium chromate, diluted in sodium chloride injection B.P., and autoclaved, has failed to tag red blood cells. In each case, the sodium chromate and ACD (acid citrate dextrose) were from stock which previously had been used successfully. The only common factor was that a particular batch of sodium chloride injection B.P. had been used throughout to dilute the sodium chromate prior to autoclaving. This saline, supplied in 20 cm^3 vials, has never been used in a successful red-cell labelling.

A sample of the saline in 20 cm^3 vials was returned to the pharmaceutical company* together with a sample of their product, supplied in 5 cm^3 vials, which had been used successfully.

In a telephone conversation with the quality control manager, we were told that from September, 1976 onwards 0.01% disodium EDTA (ethylene diamine tetraacetic acid) had been added to their sodium chloride injection B.P. to stop the precipitation of impurities on storage. The 5 cm^3 vials of saline which we had been using were manufactured before that date, but the 20 cm^3 vials contained the additive, although there was no indication of this in the labelling of the boxes or vials.

An experiment was carried out to test the effect of 0.01% disodium EDTA in saline used to dilute ^{51}Cr sodium chromate for red-cell labelling. The sodium chromate was of radioactive concentration 1 mCi/cm^3 and specific activity 100–300 μCi/μg Cr.

Two aliquots of 100 μCi ^{51}Cr were dispensed and diluted in sodium chloride injection B.P. supplied by a different pharmaceutical company. Two more aliquots of 100 μCi ^{51}Cr were dispensed and diluted in sodium chloride injection B.P. to which 0.01% disodium EDTA had been added. Four 10 cm^3 blood samples were taken from a normal volunteer into 2 cm^3 ACD and labelled in the standard way. The red cell labelling efficiencies are shown in Table I. The

TABLE I

THE EFFECT OF 0.01% DISODIUM EDTA IN SALINE ON THE EFFICIENCY OF ^{51}CR RED CELL LABELLING

	First wash % ^{51}Cr in		*Second wash* % ^{51}Cr in	
	Red cells	Washings	Red cells	Combined washings
^{51}Cr diluted in saline—autoclaved	97.5	2.5	96.0	4.0
^{51}Cr diluted in saline—not autoclaved	96.0	4.0	93.5	6.5
^{51}Cr diluted in saline—+0.01% EDTA—autoclaved	67.0	33.0	57.0	43.0
^{51}Cr diluted in saline—+0.01% EDTA—not autoclaved	89·5	10.5	89.5	10.5

---

*Pharmaceutical Manufacturing Company, West Houghton, Lancs. The company has since advised us that they have discontinued this addition.

labelling efficiency is seen to be lower in the presence of EDTA, but when the sodium chromate is autoclaved in saline containing 0.01% disodium EDTA it is converted to a form which does not label the red cells. Although 67% ^{51}Cr is present after one wash, more is removed by further washings.

These 20 cm^3 vials of sodium chloride injection B.P. were in general use in the radioisotope dispensary for several months during 1977, coinciding with a period when the labelling efficiency of some other compounds was on occasions inexplicably low. However, we cannot say definitely that this product was the cause of these latter problems.

The use of sodium chloride solutions containing a chelating agent is unacceptable in most radiopharmaceutical preparations, especially for those involving the manipulation of radionuclides in cationic form. The concentration of radionuclide cations in most preparations lies in the nano-micromolar range; thus the addition of as little as 1 cm^3 sodium chloride containing 0.01% (approximately 0.25 millimoles/dm^3) EDTA to 10 cm^3 of radiopharmaceutical will result in a molar excess of chelating agent over radionuclide ranging from about 10 to more than 10000, which is sufficient to interfere with many labelling procedures.

Although the British Pharmacopoeia Monograph on sodium chloride injection does not specifically authorize the addition of any stabilising agent or other additives, it appears that manufacturers may be adding small quantities of substances to this product without declaring the additives on the package or vial labels. In consequence, it is no longer safe to assume that sodium chloride injection B.P. is necessarily of acceptable quality for radiopharmaceutical work.

Yours, etc.,
ELIZABETH A. HARBOTTLE,
D. M. TAYLOR.

Nuclear Medicine Department,
Royal Marsden Hospital,
Downs Road, Sutton, Surrey,
and
Institute of Cancer Research,
Clifton Avenue,
Sutton, Surrey.

REFERENCES

British Pharmacopoeia 1973. Sodium chloride injection, p. 427 (Pharmaceutical Press, London).

An "error" in the "Pike-Alper" analysis

THE EDITOR, SIR,

During a recent attempt to write my own computer program for a "Pike-Alper" dose modification analysis of oxic and hypoxic radiation cell survival data (Pike and Alper, 1964) I noted an error in one of the equations.

The residual sum of squares, R_2, for the three parameter hypothesis (common value for the extrapolation number) is given as

$$\begin{aligned} R_2 = {} & \Sigma y^2 + \Sigma z^2 \\ & -((\Sigma x^2)(\Sigma w^2)(Y+Z)^2 \\ & -2X(\Sigma w^2)(\Sigma yx)(Y+Z)+(n+k)(\Sigma w^2) && (3) \\ & -W^2(\Sigma yx)^2+2WX(\Sigma yx)(\Sigma wz) \\ & -2W(\Sigma x^2)(\Sigma wz)(Y+Z)+(n+k)(\Sigma x^2) && (5) \\ & -X^2(\Sigma wz)^2)/Q \end{aligned}$$

The second terms in lines 3 and 5 of this equation are not correct and should read as follows:

2nd term line 3 $(n+k)(\Sigma w^2)((\Sigma yx)^2)$
2nd term line 5 $(n+k)(\Sigma x^2)((\Sigma wz)^2)$

In both cases the square of the product sum was omitted in the manuscript.

Yours, etc.
J. V. WATSON.

M.R.C. Unit of Clinical Oncology,
The Medical School,
Hills Road,
Cambridge CB2 2QH.

REFERENCE

PIKE, M. C., and ALPER, T., 1964. A method for determining dose-modification factors. *British Journal of Radiology*, *37*, 458–462.

Where should a film badge be worn?

THE EDITOR—SIR,

I wish to respond to the question poised by your correspondent, Dr. Bray, and the response by Dr. Sear. Viz: Whether a film badge should be worn over or under a lead apron.

The National Council on Radiation Protection and measurements (NCRP) states that for the purpose of setting a maximum permissible dose (MPD) for occupationally exposed persons, "the critical organs are considered to be the gonads, the lens of the eye, and red bone marrow". In my opinion, the purpose of the film badge is to estimate the dose to these organs. Obviously, a lead apron will shield the gonads and most of the active red bone marrow. However, the lens of the eye is seldom protected. The practice of wearing the film badge at the collar outside the film badge is an attempt to measure the maximum dose to the organ considered as critical by NCRP, *i.e.*, the lens of the eye.

This practice tells us little about the dose to the gonads or the red bone marrow, as Dr. Sear points out. We can assume that the dose to these organs is no greater than the film badge reading. The purpose of personnel monitoring is to detect over-exposure of critical organs, therefore, we can reach the required results by knowing the maximum dose to which the body, or some part of it, has been exposed. If that dose is well below the MPD, we have attained the goal. If it is near the MPD, then two or more badges should be worn at appropriate locations.

The location of the personnel monitor has not been arbitrarily chosen. The above represents the reasoning followed at our institution. I trust that it has shed more light on the question; however, I suspect that the controversy over where to wear a film badge will never be settled.

Yours, etc.,
F. FAW,

Department of Radiology & Nuclear Medicine,
Arnot-Ogden Memorial Hospital.
Elmira,
New York 14901, USA.

REFERENCES

BRAY, J. F., 1977. Where should a film badge be worn? *British Journal of Radiology*, *50*, 528.
SEAR, R., 1977. Where should a film badge be worn? *British Journal of Radiology*, *50*, 766.
NCRP, 1971. *Basic Radiation Protection Criteria*, Report 39, p. 89, (National Council of Radiation Protection and Measurements, Washington, D.C.)

Where should a film badge be worn?

THE EDITOR—SIR,

In his letter published in the issue of March, 1978, Dr. M. W. Herman advises residents to wear their monitoring film on their collars outside the lead apron to monitor whole body radiation under normal conditions, and quotes the NCRP (1968) MPD limit for the lens of the eye as 5 rem.

There is no MPD laid down for the lens of the eye in the Code of Practice used in the United Kingdom (1972 edition) other than that for any single organ, excluding gonads, red bone-marrow, bone, thyroid and skin of whole body, which is 15 rems per annum, a figure derived from the recommendations of the ICRP (1965). Publication 26 of the ICRP (1977) however, increases this figure to 30 rems per annum, so that it is difficult to sustain the contention that the MPD for the lens of the eye should be 5 rem.

Furthermore, para 2.4.2 of the U.K. Code of Practice clearly states that an individual dosemeter should normally be worn at chest or waist level underneath the protective apron.

Where there is any reason to suspect that doses to unprotected parts may approach the maximum permissible doses, the Radiological Protection Adviser must carry out a radiation survey of the department and arrange for the wearing of additional dosemeters if he considers this to be necessary.

It is apparent, therefore, that the advice given by Dr. Herman is contrary to U.K. practice.

Yours, etc.,
D. Gifford

Department of Medical Physics (Radiation Protection),
Bristol General Hospital
Guinea Street,
Bristol BS1 6SY.

REFERENCES

Code of Practice for the Protection of Persons against Ionising Radiations arising from Medical and Dental Use, 1972. (H.M. Stationery Office, London).

International Commission on Radiological Protection. Publication 9, 1966. *Recommendations of the ICRP* (Pergamon Press, Oxford).

International Commission on Radiological Protection. Publication 26, Vol. 1, No. 3, 1977. *Recommendations of the ICRP* (Pergamon Press, Oxford).

NRCP Report No. 33. 1968, *Medical X-ray and Gamma-ray Protection for Energies up to 10 MeV*. p. 41 (Washington).

(*Eds: This correspondence is now closed.*)

Appeal for certain back issues

If you have copies of any January, March and June, 1977 issues of this journal (BJR Vol. 50, 589, 591, 594) which you do not require could you please return them to the British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England, for redistribution to subscribers who are unable to obtain copies.

The Institute will refund second class postage, plus any prepayments you have made for the issues you return (only applies to January, March and June, 1977 numbers).

1978, *British Journal of Radiology*, *51*, 559–561 JULY 1978

Proceedings of the British Institute of Radiology

Abstracts of papers presented at the Radiobiology Work-in-Progress meeting held on February 17, 1978 in The Reid-Knox Hall, Institute House, 32 Welbeck Street, London, W1

An oxygen dependent X-ray lesion in the cell wall of *E. coli* B/r sensitive to penicillin, by N. E. Gillies, F. I. Obioha and H Ratnajothi.
Dose rate effects in *escherichia coli* K-12 and repair deficient mutants, by H. A. Harrop, R. L. Maughan, B. D. Michael and W. D. Rupp.
A study of the effects of very low doses of ^{60}Co γ rays on the frequency of satellite association of human acrocentric chromosomes, by M. Tariq Khokhar, T. Min and J. A. Houghton.
In vitro model for the study of thyroid radiobiology, by J. F. Malone, M. K. O'Connor, M. J. Cullen and M. Moriarty.
The induction of radioresistance by cytosine arabinoside in mouse intestine, by T. A. Phelps and N. M. Blackett.
Measurement of intestinal cryptogenic cell number using various cytotoxic agents, by J. V. Moore.
Effects of fractionated radiotherapy on the mucosal surface of the mouse intestine, by K. Carr, R. Hamlet, A. H. W. Nias and C. Watt.
Changes in the architecture of blood vessels in the rat brain after local irradiation, by J. W. Hopewell, H. S. Reinhold, J. Wilkinson and B. Blackiewicz.

Reprints of these abstracts may be obtained free on application to The Managing Editor, BRITISH JOURNAL OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG (01–935 6867).

AN OXYGEN DEPENDENT X-RAY LESION IN THE CELL WALL OF *E. COLI* B/r SENSITIVE TO PENICILLIN

By N. E. Gillies, F. I. Obioha and H. Ratnajothi

The Middlesex Hospital Medical School, London W.1

In recent years evidence has been accumulating that radiation lesions which are particularly sensitive to the presence of oxygen at the time of exposure occur in the membranes of cells (Alper, 1970; Cramp *et al.*, 1972). To detect lesions in the cell walls of *E. coli B/r*, the interaction of damage caused by X rays with that produced by penicillin, an inhibitor of cell wall synthesis, was studied. The bacteria were X-irradiated under aerobic or anaerobic conditions and then incubated immediately afterwards in nutrient broth containing penicillin, at a concentration of the antibiotic which on its own did not allow cell division or cause killing over a four hour period. After X-irradiation in the presence of oxygen, incubation with penicillin significantly enhanced the fraction of bacteria which were killed. However, no increase in cell killing was induced by penicillin in cells which had been X-irradiated under anoxia or which had been exposed to ultraviolet light (260 nm). When incubation with penicillin was delayed for two hours after X-irradiation in the presence of oxygen, no enhanced killing was observed, indicating that removal of the oxygen-sensitive radiation lesion had occurred during that time. Because the action of penicillin is localized in the peptidoglycan layer of the bacterial cell wall, it is suggested that the X-ray lesion, produced only in the presence of oxygen and which renders the cells more sensitive to penicillin, may also be associated with the same site.

DOSE RATE EFFECTS IN *ESCHERICHIA COLI* K-12 AND REPAIR DEFICIENT MUTANTS

By H. A. Harrop, R. L. Maughan, B. D. Michael and W. D. Rupp*

Cancer Research Campaign Gray Laboratory
Mount Vernon Hospital, Northwood
Middlesex HA6 2RN

We have compared the effects of dose-rate on the survival of *E. coli* K-12 AB1157 and some related repair deficient mutants under oxic and anoxic irradiation conditions. The radiation intensities ranged from repetitive 2 μs electron pulses of 7 mGy each from a linear accelerator up to single 5 ns electron pulse of 70 Gy from a field emission source. In the wild type AB1157, in JG64 *polA* and in AB1886 *uvrA*, no effect of changing dose-rate was detected, either under oxic or under anoxic conditions. In AB2463 *recA* the anoxic radiosensitivity was found to increase slightly at high dose rate and in AB2480 *uvrA recA* a much larger increase in anoxic radiosensitivity was found at high dose rate; in neither of these two strains was any detectable dose-rate dependence of radiosensitivity found under oxic conditions.

The influence of high dose-rate in the above strains parallels that of radiosensitization by triacetoneamine-N-oxyl (TAN). The strains that under anoxia are more sensitive at high dose-rates are under anoxia also more effectively sensitized by TAN. In AB2480 at high dose-rate oxygen protects (*i.e.* OER < 1) and in the same strain oxygen protects against radiosensitization by TAN. These findings appear consistent with the sensitizing effect observed at high dose-rate being due to radiation-induced non-lethal radicals reacting with potentially lethal damage sites in a manner similar to that believed to operate in radiosensitisation by TAN.

A STUDY OF THE EFFECTS OF VERY LOW DOSES OF COBALT 60 GAMMA RAYS ON THE FREQUENCY OF SATELLITE ASSOCIATION OF HUMAN ACROCENTRIC CHROMOSOMES

By M. Tariq Khokhar, T. Min and J. A. Houghton

Cytogenetics Unit, Department of Microbiology,
University College, Galway, Ireland

The most common chromosomal abnormality in live-born children is trisomy 21, a condition resulting from chromosome non-disjunction during nuclear division. It has been suggested that the satellite association of the acrocentric chromosomes may help to keep these chromosomes together during division and so lead to an increased risk of non-disjunction. This hypothesis has stimulated studies into satellite association in normals, and in Down's syndrome and other chromosomally abnormal populations. Some studies have suggested that parents of Down's syndrome patients show an increased frequency of satellite association whilst others have contradicted this finding. Assessment of clinical data available on Down's syndrome has suggested that there is an increased incidence of Down's syndrome births in mothers who were exposed to ionizing radiations for radiodiagnostic or radiotherapeutic reasons. This implies that ionizing radiations might lead to increased chromosome non-disjunction during nuclear division and hence may also have increased the frequency of satellite association. To determine whether irradiation might lead to an increased frequency of satellite association, human blood lymphocytes were irradiated with various doses of ^{60}Co γ rays ranging between 5 and 80 rad. The frequency and patterns of satellite association in metaphase preparations from irradiated and unirradiated control samples were determined using the criteria of Zang and Back (1968). Blood samples were used from normal males and females, male and female Down's syndrome patients and also the parents of Down's syndrome patients. Irradiations were performed at 37°C and at room temperature. The cultures of blood were harvested after 48 hours incubation period at 37°C when the frequency of satellite association was found to be at its maximum in unirradiated controls. The results do not indicate a dose response relationship for an effect on the frequency of satellite association. By using the silver staining method of Goodpasture and Bloom (1975), it has now become possible to analyse the frequency and patterns of satellite association directly.

---

*Yale University, New Haven, Connecticut, U.S.A.

In vitro MODEL FOR THE STUDY OF THYROID RADIOBIOLOGY

By J. F. Malone, M. K. O'Connor, M. J. Cullen and M. Moriarty

Department of Physics, College of Technology
Kevin Street, Dublin 8,
Trinity College, Dublin 2,
Meath Hospital, Dublin 8, and
St. Luke's Hospital, Dublin 6, Ireland.

Irradiation of the thyroid is widely used for treatment of thyrotoxicosis and thyroid cancer. Despite this there has been little success in attempting to measure the radiobiological response of the gland in terms of well defined dose-effect relationships for parameters such as cell death, or decrease and alteration of cell function. A number of workers have demonstrated an apparent sigmoid survival curve for the rat thyroid *in vivo* (Greig *et al.*, 1970; Malone, 1975), and a linear dose-effect curve for the incidence of post-irradiation hypothyroidism in humans (Malone and Cullen, 1976; 1977). However, radiobiological responses demonstrated *in vivo* are complicated by seriously inaccurate dosimetry and large normal variation in the end points such as gland weight selected for assay.

To allow a more accurate approach to thyroid radiobiology we have investigated the possibility of using primary cultures of sheep thyroid cells. Existing methodology for thyroid cell cultures was inadequate as cell function and the characteristic morphology were retained for about one week only (Fayet and Hovsepian, 1977). This is insufficient time for the development and assay of radiation damage. We have, therefore, developed a system allowing primary monolayer culture of thyroid cells for periods of three weeks or greater. The cells can be made to undergo up to ten divisions, trap and organify iodide, and organize themselves into a follicular structure typical of the thyroid *in vivo*. This system provides an excellent opportunity for the study of thyroid radiobiology in an exact way, and can probably be extended to normal and abnormal human thyroids. The behaviour of normal cultures with respect to growth patterns, induction of follicular morphology, uptake of ^{125}I per 10^6 cells and production of iodothyronines is now well established. Initial radiation experiments indicate that, for example, cell survival after 600 rad, estimated by extrapolation of growth curves, is approximately 25%.

THE INDUCTION OF RADIORESISTANCE BY CYTOSINE ARABINOSIDE IN MOUSE INTESTINE

By T. A. Phelps and N. M. Blackett

Institute of Cancer Research, Clifton Avenue
Sutton, Surrey

The effect of radiation on normal tissues can be mitigated by prior treatment with various agents which are themselves cytotoxic. One such agent is the S-phase specific drug cytosine arabinoside (ara-c). Administration of ara-c immediately before radiation results in a dose dependent decrease in intestinal clonogenic cells as assayed by the microcolony technique of Withers and Elkind, indicating that clonogenic cells are sensitive to ara-c. If the drug is given 12 h before irradiation, however, survival of microcolonies increases in a dose dependent fashion up to 200 mg/kg. Radiation survival curves obtained immediately or 12 h after 200 mg/kg ara-c indicate that the D_0 rises from a level of 1.5 ± 0.09 Gy at 0 h to 3.14 ± 0.33 Gy at 12 h after the drug. Microcolony survival increases from a minimum of 0.002 at 0 h to surpass the control level of 0.008 due to 14 Gy alone by 4 h. It then reaches a maximum of 0.50 at 12 h, after which microcolony survival returns to near the γ-control level by 24 h.

Labelling and mitotic indices confirm the induction of synchrony by ara-c. The presence of a second peak in labelled cells at 20 h, however, is not accompanied by a second peak in microcolonies and therefore it is not possible to conclude that the radioresistance induced by ara-c results from late S resistance of synchronized cells. Furthermore, insertion of a first dose of 9 Gy immediately after ara-c in a split dose survival curve does not alter the timing of the 12 h microcolony peak, even though 9 Gy might be expected to cause considerable mitotic delay. Finally, the surviving clonogenic cells after high doses of radiation must be the most resistant cells in the tissue and so a further increase in D_0 as a result of ara-c cannot be due to progression of the cells to some other part of the cell cycle.

The hypoxic sensitizer misonidazole has been used to show that the changes brought about by ara-c are not due to hypoxia.

Experiments were also carried out which demonstrate that ara-c causes radioresistance at doses as low as 3 Gy as well as doses up to 21 Gy.

MEASUREMENT OF INTESTINAL CRYPTOGENIC CELL NUMBER USING VARIOUS CYTOTOXIC AGENTS

By J. V. Moore

Paterson Laboratories, Christie Hospital and
Holt Radium Institute, Manchester M20 9BX

The intestinal crypt microcolony assay (Withers and Elkind, 1970) is held to measure the response to damage of a population of epithelial cells ("cryptogenic" cells), each of whose members can regenerate an entire crypt. As assayed by the effects of low LET irradiation, recent estimates of the mean number of cryptogenic cells per murine jejunal crypt (A) have ranged from 80 to 140. For alklating agents injected intraperitoneally into BDF_1 mice, the extrapolation numbers on the curve of crypt survival (AE, assumed to equal A × recovery factor per cell) were invariably lower than those for radiation. For bis-chloroethyl nitrosourea, AE$\approx$140, A$\approx$5; mustine hydrochloride, AE$\approx$4, A$\approx$1; isopropylmethane sulphonate, AE$\approx$2.5, A$\approx$2. The reciprocals of the slopes for survival of cryptogenic cells were respectively $\approx$20, 2, and 400 mg kg^{-1} of body weight. The former two imply a greater sensitivity to drug than that of unstimulated stem cells of the bone marrow of these mice.

EFFECTS OF FRACTIONATED RADIOTHERAPY ON THE MUCOSAL SURFACE OF THE MOUSE INTESTINE

By K. Carr*, R. Hamlet†, A. H .W. Nias†
and C. Watt*

**Department of Anatomy, University of Glasgow
and †Glasgow Institute of Radiotherapeutics
Belvidere Hospital, Glasgow G31 4PG*

Three fractionated radiotherapy schedules were investigated using the microcolony technique of Withers and Elkind (1970) and scanning electron microscopy of the mucosal surface, in an attempt to investigate features of irradiation damage to the whole of the intestinal mucosa at dose levels commonly used in clinical practice.

Despite variations in the qualitative observations, there was a marked difference in the three schedules between damage expressed as crypt counts and that seen by scanning electron microscopy. With the first schedule (300 rad/day), high numbers of regenerating crypts (96, compared with 120 in controls) were associated with severe mucosal damage, whereas the second schedule (450 rad/day) produced a reduction in crypt number (85) but a low level of damage to the surface mucosa. In the third schedule (250 rad three times/day), there was good agreement between a low crypt count (18) and severe mucosal damage.

These results demonstrate that doses which do not seriously disturb the proliferative capacity of a biological system might considerably disrupt its physiological function with the possibility therefore of producing effects remote from the site of injury.

CHANGES IN THE ARCHITECTURE OF BLOOD VESSELS IN THE RAT BRAIN AFTER LOCAL IRRADIATION

By J. W. Hopewell, H. S. Reinhold*,
J. Wilkinson and B. Blackiewicz*

*Research Institute, Churchill Hospital, Oxford
and *TNO Radiobiological Institute, Rijswijk,
The Netherlands*

Local irradiation of the brain of rats with doses of the order of 2000 rad results in significant life-shortening. Histological investigations of post-mortem material provided evidence of focal areas of necrosis which were associated with clearly defined vascular lesions. The purpose of the present study was to determine the time course of the first appearance of these vascular lesions and to investigate quantitatively general changes in the vascular architecture in the preceeding latent period. Perfusion, fixation and filling of the vascular system of the brain with pigment (luconyl blue) assisted in these investigations.

Examination of cleared coronal slices of the brain demonstrated that gross vascular lesions were first found after a latent period of 12 months or longer. The majority of these lesions were in the mixed grey and white matter regions of the mid-brain. Smaller numbers of lesions were found in the cerebral cortex and these were restricted to the deeper layers.

Quantitative measurements of changes in the vascular architecture of the cerebral cortex were made from histological sections. The analysis was aided by the use of a Quantimet shape analysing computer. Significant changes in the vascularity of the cerebral cortex were observed nine months after irradiation with a dose of 2000 rad. This involved an increase in the blood volume index, mainly due to an increase in the number of vessels more than 8 μm in diameter. The greatest effect was in the deeper layers of the cortex.

Vaso-dilation would explain previous reports of increased blood flow as a consequence of local brain irradiation. These findings are discussed in terms of known auto-regulatory response of the brain to hypoxia.

REFERENCES

ALPER, T., 1970. Mechanisms of lethal radiation damage in cells. *Proceedings of the Second Symposium on Microdosimetry. Stresa (Italy)*, 5–35.

CRAMP, W. A., WATKINS, D. K., and COLLINS, J., 1972. Effects of ionizing radiation on bacterial DNA-membrane complexes. *Nature new Biology*, *235*, 76–77.

FAYET, G., and HOVSEPIAN, S., 1977. Active transport of iodide in isolated porcine thyroid cells. *Molecular and Cellular Endocrinology*, 7, 67–78.

GOODPASTURE, C., and BLOOM, S. E., 1975. Visualisation of nucleosus organiser regions in mammalian chromosomes using silver staining. *Chromosoma*, *53*, 37–50.

GREIG, W. R., SMITH, J. F. B., ORR, J. S., and FOSTER, C. J., 1970 Comparative survivals of rat thyroid cells *in vivo* after ^{131}I, ^{125}I and X-irradiations. *British Journal of Radiology*, *43*, 542–548.

MALONE, J. F., 1975. The radiobiology of the thyroid. *Current Topics in Radiation Research*, *10*, 263–368.

MALONE, J. F., and CULLEN, M. J., 1976. Hypothyroidism after ^{131}I therapy: a two mechanism hypothesis. *Lancet ii*, 73–75.

1977. Hypothyroidism after ^{125}I therapy. *Annals of Internal Medicine*, *86*, 823–824.

WITHERS, H. R., and ELKIND, M. M., 1970. Microcolony survival assay for cells of mouse intestinal mucosa exposed to radiation. *International Journal of Radiation Biology*, *17*, 261–267.

ZANG, K. D., and BACK, ELKE, 1968. Quantitative studies on the arrangement of human metaphase chromosomes. *Cytogenics*, 7, 455–470.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1.00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (i.e. April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

World Federation of Nuclear Medicine and Biology

To be held September 17–21, 1978. The Second International Congress of the World Federation of Nuclear Medicine and Biology will provide an international forum for the exchange of scientific information, the dissemination of knowledge, and the world-wide promotion of the discipline of nuclear medicine.

The Scientific Symposia will encompass all the activities and interests of nuclear scientists and physicians: medical and health physics; instrumentation; data analysis; radiochemistry; radioassays; *in vivo* and *in vitro* biochemical and physiological measurements; radiopharmaceuticals; functions and disorders of the cerebral, pulmonary, cardiovascular, abdominal, renal, peripheral vascular, bone, joint endocrine, and metabolic systems.

There will be three pre-meeting courses: cardiovascular nuclear medicine; positrons, cyclotrons, and tomography; nuclear medicine in developing countries. During the meeting, there will be review teaching sessions on the state of the art in clinical nuclear medicine.

The technologist programme will include considerations of quality assurance, recruitment, education and career opportunities.

The meeting has been designed to afford maximum opportunities for exchanges of ideas and views among nuclear colleagues.

Morning activities will provide a plenary session, time for small discussion groups, and for visiting the exhibits of equipment and radiopharmaceutical manufacturers.

Afternoons will be devoted to contributed papers, poster sessions, panels and mini-symposia.

Further information from Dr. H. N. Wagner, President, WFNMB Second International Congress, 1629 K Street, N.W., Suite 700, Washington, D.C., 20006, USA.

Nuclear Medicine in Pediatrics

A joint meeting of The British Institute of Radiology and the Edinburgh College of Physicians will be held in Edinburgh on October 20, 1978.

One session will be devoted to renal disease, one to cardiac and respiratory disease and one to general topics. Dr. David Gilday will be reviewing the clinical application on nuclear medicine in children.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

British Medical Ultrasound Society Annual Meeting and Exhibition

To be held November 27–28, 1978 at the Civic Centre, Newcastle upon Tyne. Potential exhibitors are invited to contact A. J. Hall, Queen Mothers's Hospital, Glasgow, G3 8SH (041-399 8888 ext. 548).

Further details from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Workshop on the use of Computerized Tomographic Scanners in Radiotherapy

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

4th Congress of the European Association of Radiology

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

Quantitation of Tumour Response: a Critical Appraisal

The the L. H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a *critical* appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Correspondence (*continued*)

Page

The use of sodium chloride injection B.P. in the preparation of radiopharmaceuticals. 556
Elizabeth A. Harbottle and D. M. Taylor
An "error" in the "Pike-Alper" analysis.
J. V. Watson
Where should a film badge be worn?
F. Faw
Where should a film badge be worn?
D. Gifford

Proceedings of the British Institute of Radiology. 559
Radiobiology Work-in-Progress meeting (February 17, 1978)

Forthcoming events and other notices. 562

Book reviews

The hospital preparation of radiopharmaceuticals 483
Radiology of the liver 493
Computerised cranial tomography 497
Progress in pediatric radiology. Skull, spine and contents. Part II, Clinical aspects. 502
Radiology and injury in sport 506
Radiography in obstetrics 514
Bone marrow transplantation and other treatment after radiation injury 523
Nuclear medicine: clinical and technological bases 523
Erkrankungen des Magens (Diseases of the stomach) 527
Skeletal projections for diagnostic radiology 538
Nuclear ophthalmology 538
An atlas of cardiology: electrocardiograms and chest X-rays 549

4th South African National and International Radiological Congress

31st August – 6th September 1978
Johannesburg

MEDICAL CONFERENCE TRAVEL SERVICE (in association with Rand Travel, the official South African agent) have organised special inclusive prices for delegates to attend the above important Congress.
For full details including pre and post congress tours please contact:

Medical Conference Travel Service
24 Preston Street,
BRIGHTON BN1 2HN
(Tel. 0273 203111)
Parent Company: Martlet Travel Ltd. (CAA ATOL 257B)

VOL 51 NO 607 JULY 1978

The British Journal of Radiology

Contents

Page

Continental notebook. Review of the continental radiological literature. 481
W. A. Fuchs

Abdominal contrast tomography in the evaluation of the gall-bladder and biliary tract (with emphasis upon jaundiced patients). 484
L. Dalla Palma, M. Bazzocchi and M. di Pietrantonio

Subpulmonary pneumothorax. 494
A. Schulman and R. B. Dalrymple

Lateral lumbar discography. 498
J. A. McCulloch and G. Waddell

The effect of radiology electives on career choice at McMaster University. 503
M. S. F. McLachlan and M. Herzig

Dosimetry of cathetron applicators in intracavitary therapy. 507
A. V. Santhamma and K. R. Das

Radiation damage to the rat spinal cord: the effect of single and fractionated doses of X rays. 515
Ann White and Shirley Hornsey

The response of *E. coli* AB2463 recA to fast neutron beams with mean energies in the range 4 to 27 MeV. 524
J. L. Redpath

Technical notes. 528
  Colonic lavage prior to barium enema—a comparison of two techniques.
    E. Bresnihan, F. T. de Dombal, G. J. S. Parkin, S. E. W. Smith, S. Fakes and J. Horrocks
  Reciprocity law failure with film/screen combinations for mammography.
    W. W. Seelentag and W. Panzer
  Good thermal dosimetry is essential to good hyperthermia research.
    J. E. Robinson, G. H. Harrison, W. A. McCready and G. M. Samaras
  A linear transform of the multi-target survival curve.
    J. V. Watson

Case reports. 539
  Essential osteolysis of carpal and tarsal bones.
    P. H. Amin and A. N. W. Evans
  Complications of "Chiba" needle transhepatic cholangiography.
    H. Moskowitz, C. Polivy, A. W. Hackford, N. Mann and M. Josel
  Multicystic kidney—an example of bilateral involvement in an adult.
    C. D. R. Flower and P. G. Kitchener
  Visualization of abnormal adrenal uptake of 19-iodocholesterol in Conn's syndrome.
    D. M. Thomson, P. Dovey and J. B. Davis
  Renal involvement with non-Hodgkin's lymphoma: investigation of a recent case.
    N. W. Garvie, J. M. G. Chu, J. Nuttall and V. R. McCready
  Pleural cyst of the mediastinum.
    D. L. Klein

Short communications. 550
  Measurements of the OER and RBE for neutrons generated by 70 MeV protons on lithium.
    M. Guichard, J. Gueulette, G. Laublin, A. Wambersie and E. P. Malaise
  Radioprotection of mammalian cells by procaine.
    T. M. Yau and S. C. Kim

Correspondence. 553
  Thyroid irradiation and the new ICRP dose limits.
    J. F. Malone
  Examination of small bowel by double contrast technique.
    T. G. Girdwood

(*Continued, inside back cover*)

Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0007-1285
12306

August 1978

Acc.
19.2.79

THE BRITISH JOURNAL OF RADIOLOGY

X-ray diagnosis
Radiation oncology
Nuclear medicine
Ultrasound
Radiological physics
Radiobiology
Radiation protection
and related disciplines

LIBRARY

Published by
The British Institute of Radiology

The British Journal of Radiology

FOUNDED 1896

The Editorial Committee consists of:

The Editors:
D. K. BEWLEY, M.A., PH.D. F. STARER, F.R.C.P., F.R.C.R.

The Deputy Editors:
B. T. HALE, M.B., CH.B., F.R.C.R., D.M.R.T. N. W. RAMSEY, PH.D., F.INST.P.
J. ROYLANCE, F.R.C.R.
and
The Associate Editors:
A. B. AYERS, M.D., D.M.R.D., F.R.C.R.
THELMA D. BATES, M.B., CH.B., F.R.C.R., D.C.R.A.
D. COSGROVE, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. COTTRALL, B.A., M.SC., PH.D., F.INST.P.
C. D. R. FLOWER, M.A., F.R.C.P.(C), F.R.C.R.
N. E. GILLIES, B.SC., PH.D.
J. A. GLEESON, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
H. GRAVELLE, B.SC., M.B., CH.B., F.R.C.P.(E.), F.R.C.R., D.M.R.D.
J. L. HAYBITTLE, M.A., PH.D.
C. R. HILL, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. KEELING, M.A., M.SC., M.B.
I. KELSEY FRY, D.M., F.R.C.P., F.R.C.R.
B. KENDALL, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. MEIRE, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. PATTON, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. SCOTT, M.D.
T. SHERWOOD, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. VEALL, D.SC., F.INST.P.

The Associate Editors Overseas are:
P. ARMSTRONG, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
J. R. CUNNINGHAM, M.SC., PH.D. (Canada)
H. A. LUKE, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. SIM, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. STANFORD, M.A., F.INST.P. (Australia)

Managing Editor: MRS. LEE SURRY

Communications should be addressed to the Editors in accordance with the Instructions to Authors which are published in the January issue of the Journal in each year and copies of which may be obtained on application to the Managing Editor.

ADVERTISEMENTS: Communications regarding accounts should be addressed to the Institute. All other communications should be addressed to Miss Hilary Cook, Advertising Manager, The British Journal of Radiology, Advertisement Department, 24a Litchfield Street, London WC2H 9NX.

SUBSCRIPTIONS: All communications should be sent to The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England. Notification of change of address should include an old mailing label and the new address. Claims for missing copies can only be allowed if received within three months of publication date.

ANNUAL SUBSCRIPTION: (post free, payable in advance) £35·00 per annum (monthly) (U.S.A. $66). Single copies: £3·50.

Second class postage paid at New York. Mailing agents: N.Y. Expediters of the Printed Word Ltd., 527 Madison Avenue, Suite 1217, New York, N.Y. 10022, U.S.A.

The British Institute of Radiology

Incorporated by Royal Charter
Founded 1897

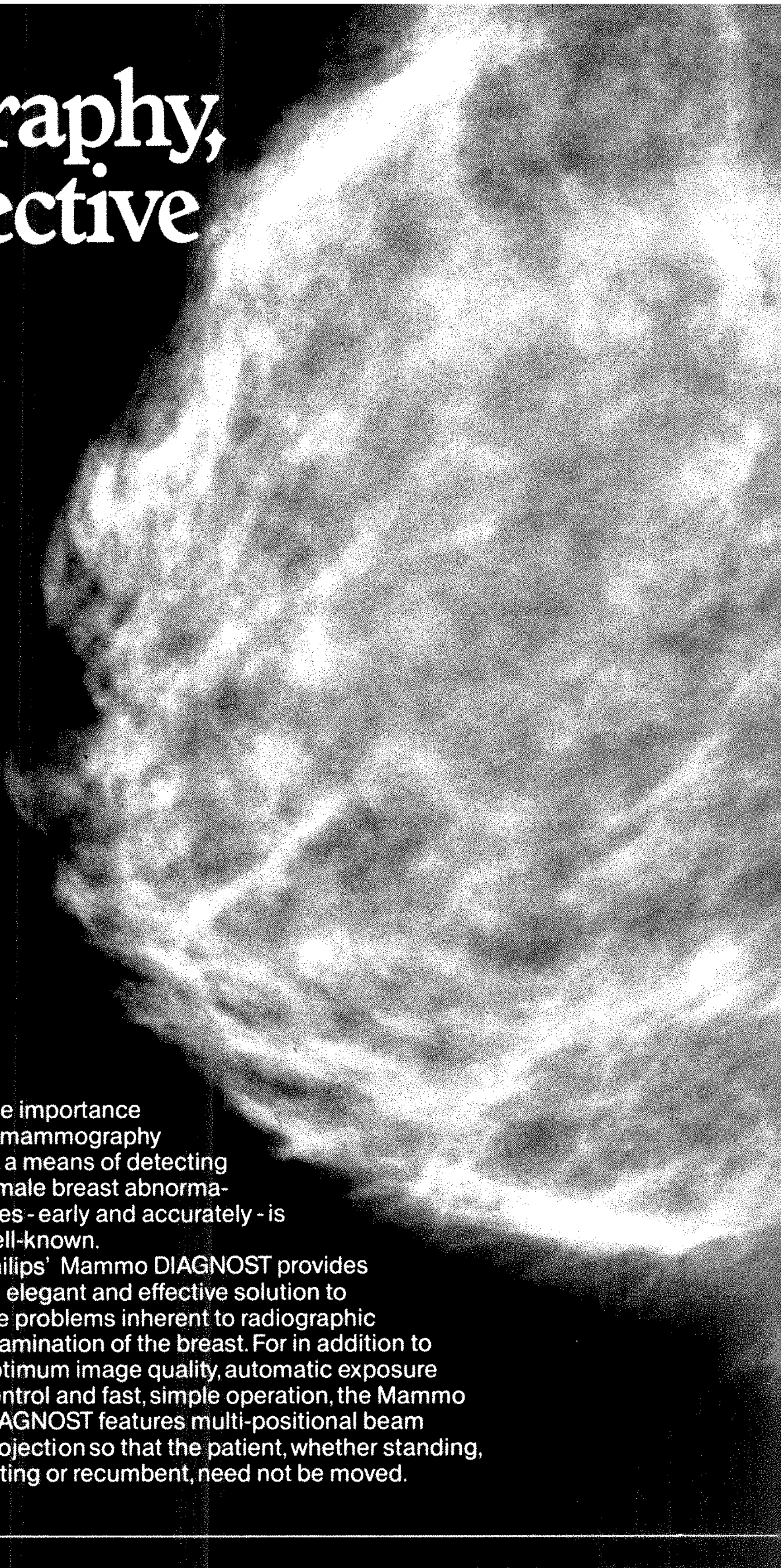
32 WELBECK STREET, LONDON W1M 7PG
Telephone: 01–935 6237 and 01–935 6867. Cable Address: "Britology, London W.1."

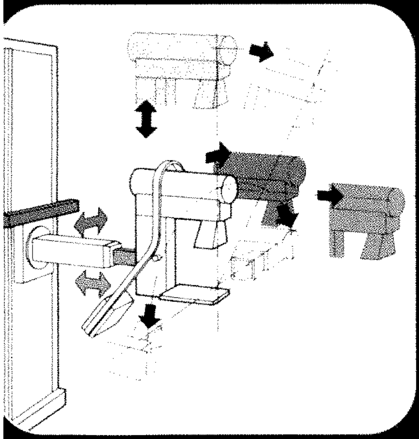
President: J. F. FOWLER, D.SC., PH.D., F.INST.P.

Hon. Secretaries:
W. HATELY, M.B., CH.B., F.R.C.P.E., F.R.C.R., D.M.R.D. P. N. T. WELLS, M.SC., PH.D., F.INST.P.
Hon. Treasurer: D. T. KERRISK

THE BRITISH INSTITUTE OF RADIOLOGY is an association of persons interested in Radiology and allied subjects. Meetings are held monthly from October until May. Particulars of membership and other information may be obtained on application to the General Secretary at the Institute.

© British Institute of Radiology, 1978





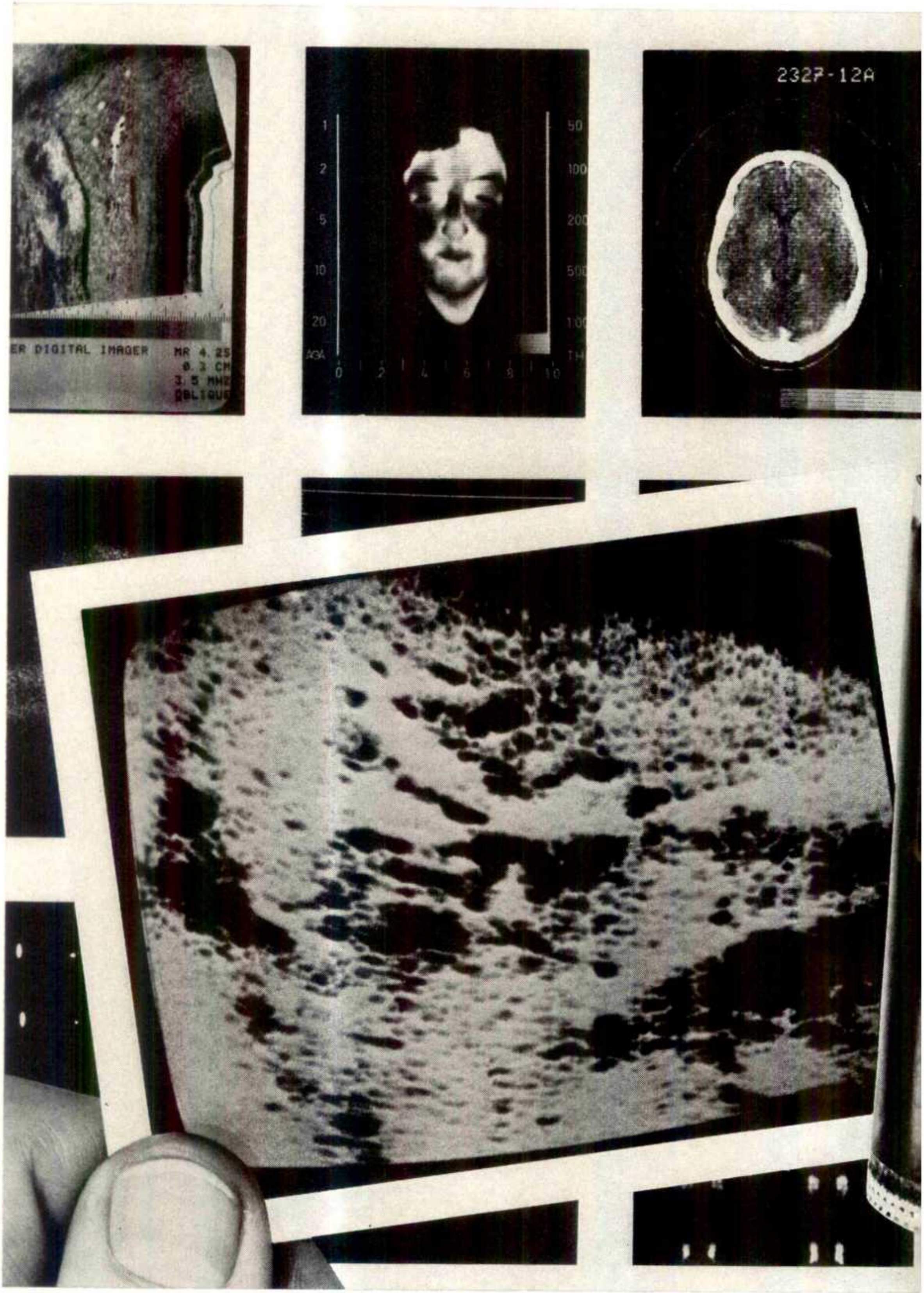
Mammography, elegant, effective

The importance of mammography as a means of detecting female breast abnormalities - early and accurately - is well-known.
Philips' Mammo DIAGNOST provides an elegant and effective solution to the problems inherent to radiographic examination of the breast. For in addition to optimum image quality, automatic exposure control and fast, simple operation, the Mammo DIAGNOST features multi-positional beam projection so that the patient, whether standing, sitting or recumbent, need not be moved.

PHILIPS

PHILIPS **Medical Systems**

For detailed information on Philips Mammo DIAGNOST, write to Philips Medical Systems Ltd.
15 Nightingale Lane, Balham, London SW12 8SX, UK, or Philips Medical Systems Division, Eindhoven, the Netherlands.


ER DIGITAL IMAGER
MR 4.25
0.3 CM
3.5 MHZ
OBLIQUE
1
2
5
10
20
AGA
0 2 4 6 8 10
50
100
200
500
100
TH
2327-12A

The diagnostic details. Instantly.

Nothing saves time like Polaroid instant photography.

You can have a fully developed picture for diagnosis from your CRT monitor in seconds.

For sheer convenience, too, there's no better way. You don't need developing and printing equipment. You don't need a darkroom or chemicals. You don't even have to leave the patient. Everything is taken care of by the self-processing film.

Part of our films' convenience is that you know instantly whether the picture you've taken is exactly right for your diagnostic needs. If not, you can retake it on-the-spot while the patient is still in place.

Polaroid self-developing films have the sensitivity, resolution, exposure latitude and grey scale capability to deliver excellent diagnostic photographs.

And one more thing-we offer you more than the speed, convenience and quality of our films. Our Technical Assistance is as close as your telephone. For more information call us on Freefone 2143 or write to Polaroid (UK) Ltd., Business & Professional Products Division, Ashley Road, St. Albans, Herts. AL1 5PR.

Polaroid

Instant films for CRT recording

'Polaroid' is a registered trademark of Polaroid Corporation,
Cambridge, Mass.,USA. Polaroid (UK) Ltd.,
Ashley Road, St. Albans, Herts. © Polaroid Corporation 1978.

Left: Ultrasound Scan. Longitudinal Examination.
Common Bile Duct and Hepatic Ducts. Patient has cancer of the Pancreas. Polaroid Type 667 film. Print size 3¼" x 4¼."

Your Kodak

rep wants to give you a helping hand

Give your rep a few minutes of your time.

And he'll help you expose a set of high definition extremity radiographs (like the one reproduced here) processed in your department in 90 seconds.

Give him a little longer and he'll demonstrate for you high information radiographs of all types. Ask him to tell you about any of these Kodak products for the radiographer.

Kodak 'Lanex' Regular Screens. This high speed rare earth system is exclusive to Kodak.

Kodak Ortho G Film. Colour sensitivity is matched to the 'Lanex' screens for optimum contrast, high information content and low dosages.

Kodak 'X-Omatic' Cassettes. Specially designed to expel air on closing, and provide excellent film/screen contact.

Kodak 'X-Omatic' Identification Camera, Model X-1-L. Allows the radiographer to record patient data on the radiograph at the point of exposure.

Kodak RP 'X-Omat' Processor, Model 101. Low cost, low noise, high speed automatic processing with cold water wash.

Kodak 'Min-R' Screen and Film. The fast, high definition film/screen combination for mammography, using rare earth phosphors.

Kodak RP 'X-Omat' Processor, Model M6A-W. Our fastest automatic processor, delivering roll and sheet film at about 167 cm per minute.

Whenever you need information, speak to your Kodak representative. You'll find he's got all the facts at his fingertips.

Kodak. We care about your image

Kodak

Kodak Lanex, X-Omatic, X-Omat, Min-R are trade marks.

Half page: 25×36 ems (Whole page: 51×36 ems)

Effective 1 September 1978

The British Journal of Radiology

The official organ of The British Institute of Radiology. Incorporated by Royal Charter

Rates for Advertisements

Page size	One Insertion £	Six Insertions £	Twelve Insertions £
Whole page	88·00	83·00	77·00
Half page	50·00	47·50	44·50
Quarter page	28·00	26·50	24·50
Eighth page	19·00	18·00	16·50
Bleed page	20·00 extra per page		
In black and standard second colour			
Whole page	127·50	122·00	100·00

Rates for four colour advertisements by arrangement

Box Number fee £1·00

Terms: Monthly Net. Series orders must be completed within a year. The right is reserved to decline or omit any advertisement. No responsibility can be accepted for the omission to insert an advertisement from any cause.

Copy must be received 5 weeks preceding the publication date, and no alterations or corrections can be made unless the amended proofs are returned before noon on the 1st of the month.

Preferential positions: Facing editorial/facing cover/inside front cover+20%

Double page spread £5·00 discount

All applications for space to be made to

Advertising Department

British Journal of Radiology

24a Litchfield Street, London WC2H 9NX. Tel. 01–836 5281

Quarter page: 25×17½ ems

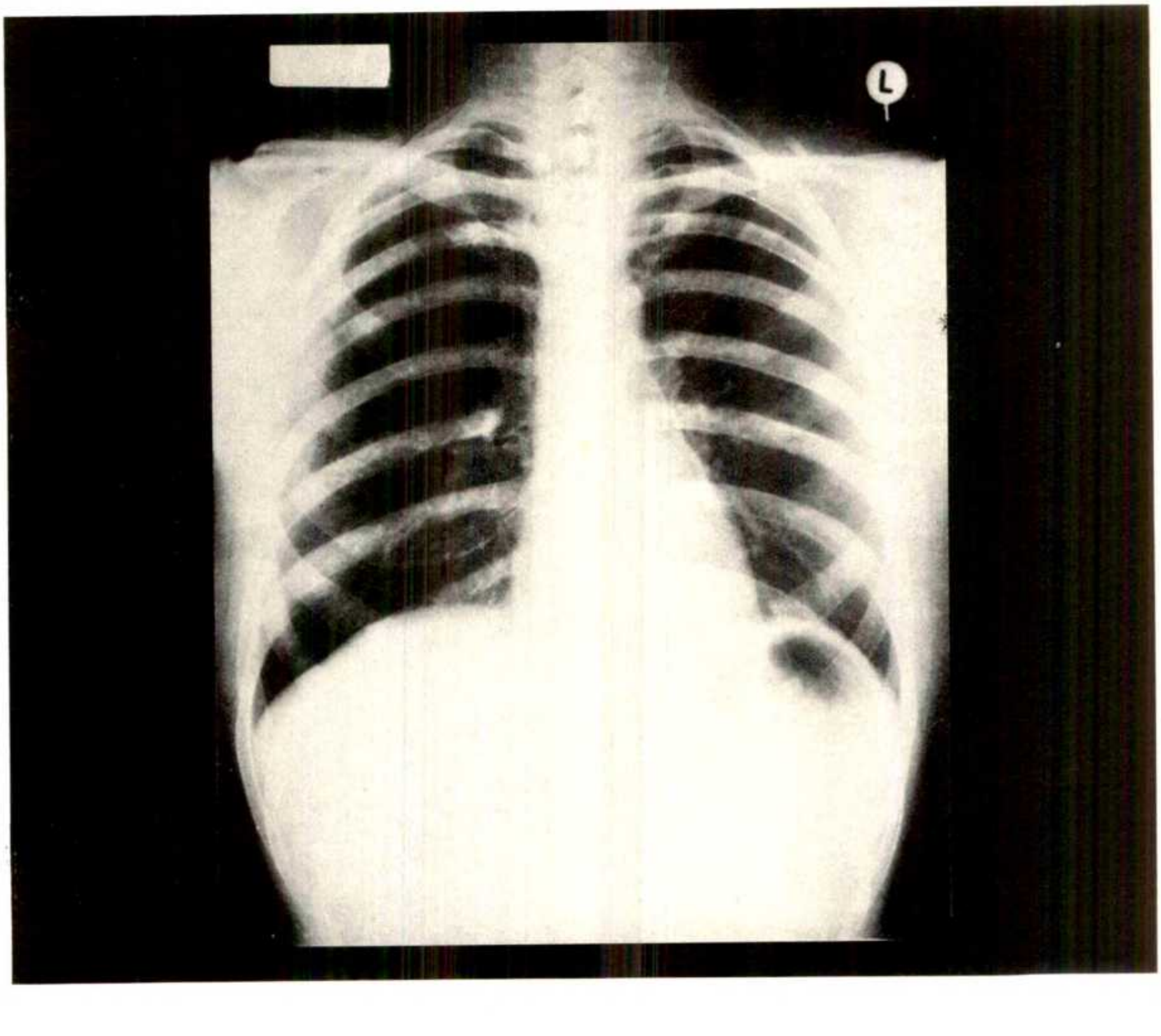
Eighth page: 12×17½ ems

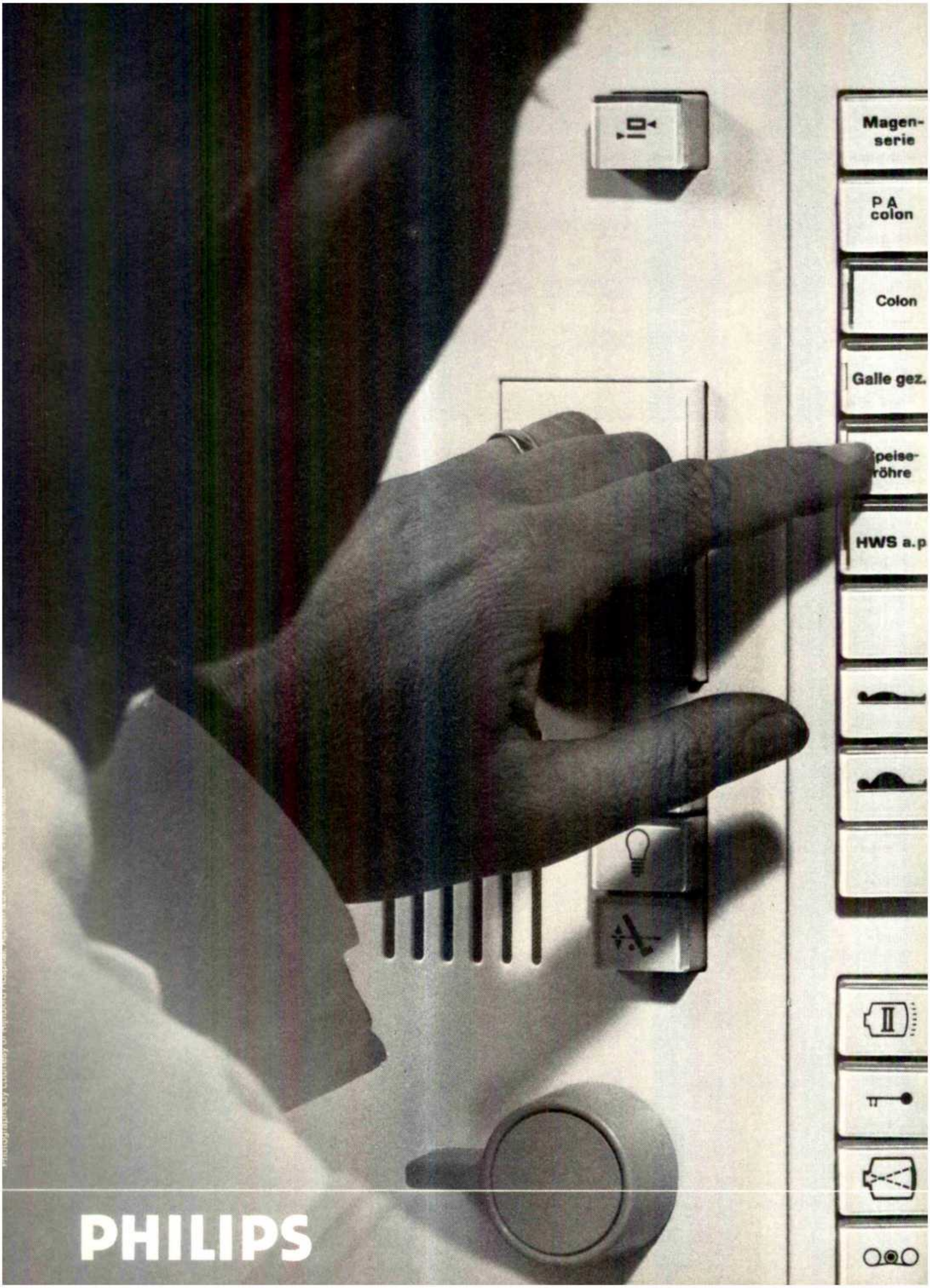
AGFA-GEVAERT

Agfa-Gevaert introduces CURIX RP1L. Specially formulated for chest radiography.

A new, low contrast, rapid processing film with particularly high exposure latitude.

Agfa-Gevaert Ltd.,
Medical X-Ray Dept.,
27 Great West Road,
Brentford, Middlesex TW8 9AX.
Tel: 01-560 2131





Photographs by courtesy of [illegible]

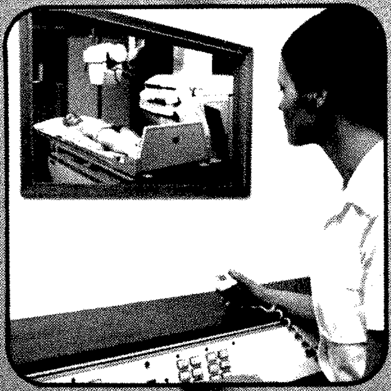
No need to shout for kVs. Modular means they're right at your fingertips.

The Philips modular generator series gives you full control of your generator while attending to the patient being examined. Controls for the modular generator are integrated in the serial changer of the DIAGNOST 73, within your natural reach so that you can select the appropriate parameters for every routine examination yourself. This system of anatomically programmed radiography leaves you free to concentrate on the patient, while retaining full control over the generator.
The modular construction allows the installation to be designed to meet your specific requirements, and to be extended as your department grows.

Modular means made to measure.

All parameters you have chosen on the serial changer are indicated on the generator desk.

For bucky work on the DIAGNOST 73, or an additional unit, the generator desk incorporates additional controls for anatomically programmed radiography. You are free to distribute the settings you require over the available push-buttons in whatever way you like.



The generators incorporate automatic kV and mA control ensuring bright, evenly illuminated fluoroscopy pictures. Moreover, the dual programme technique enables you to change instantly to full size.

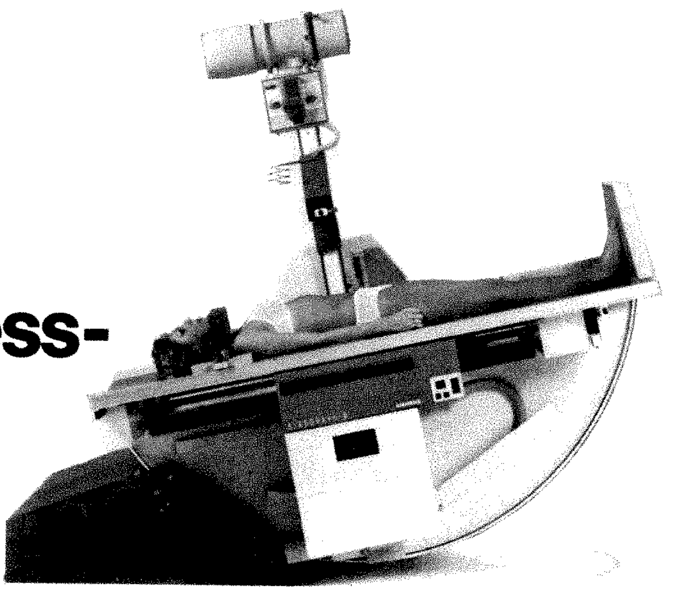
For detailed information, write to: Philips Medical Systems,
Eindhoven, The Netherlands
or Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8SX.

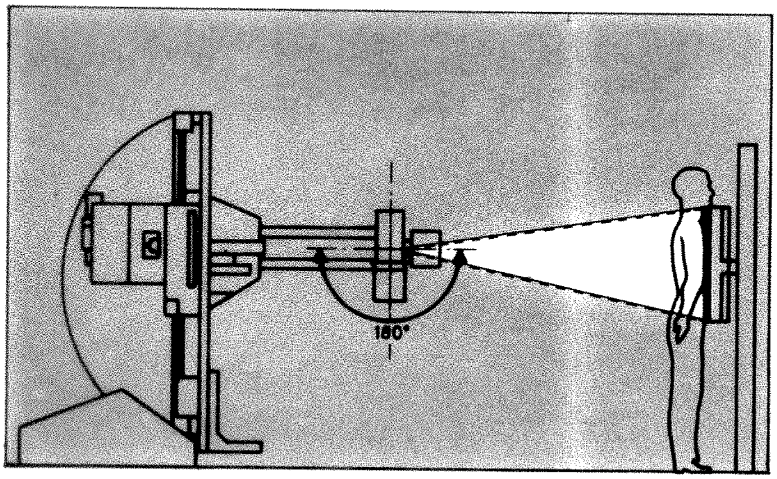
PHILIPS

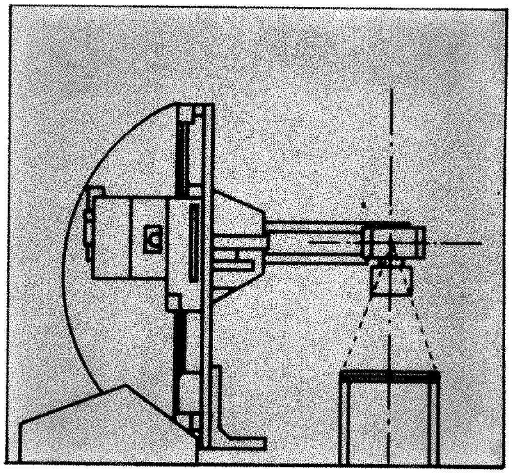
Medical Systems

SIEMENS

Versatility and cost effectiveness-the basis of the Siemens x-ray table.







The multi-purpose Siregraph B x-ray table combines the latest Siemens cost effective practice with the most up-to-date and versatile developments in x-ray technology.

The Siregraph B is a fully automatic table of compact dimensions designed to facilitate easy patient access and with the following principal features:

- Explorator – with exceptionally large cassette program.
- 90°–0°–20° indexing positions plus a full range of table-top movements in the longitudinal and lateral planes.
- Extensive tube/explorator excursion with parallax compensation for oblique angulations.
- Tomography facility in all angulations.
- Accepts up to Sirecon 2 30H triplex image intensifier and 70/100mm cameras.

The Siregraph B accommodates a swivelling x-ray tube, ideal for recumbent emergency radiography while allowing free access to the patient from all sides. Indexing positions at 0°, 90° and 180° ensure reproducible radiographic settings.

Siemens Ltd, Medical Group, Siemens House, Windmill Road, Sunbury-on-Thames, Middlesex, TW16 7HS. Tel: 09327 85691.

In the world of remote control Siemens has the answer.

Therac 20

More energy in less space.
20 MeV electrons. 18 MeV photons.

Its space requirements are surprisingly modest.
Yet, the Therac 20 Linear Accelerator from AECL has a
high energy output in both electron and photon modes.
Standard among its many features are constant
electron beam scanning for optimum dose distribution
and record and verify control for added safety.
Therac 20 is more energy in less space.
For complete information, contact AECL.

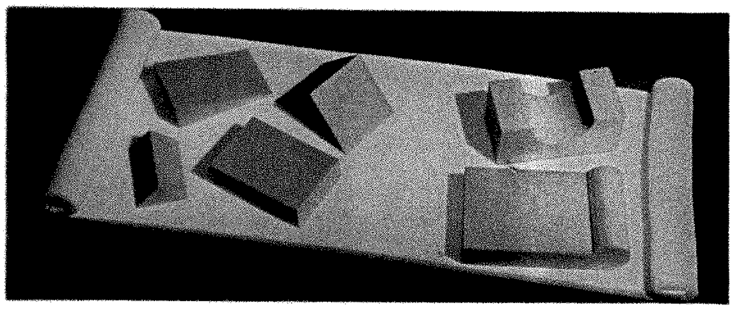
Atomic Energy
of Canada Limited
Commercial Products

P.O. Box 6300, Ottawa, Canada, K2A 3W3. Tel: (613) 592-2790.
Cable Nemota. Telex: 053-4162

polyfoam®

ANSAFONE SERVICE
operates 5pm-9am and at weekends

unique padding permits passage of X-rays without showing on the plate



A typical example of the use of Polyfoam is the provision of a warm and comfortable cover for an X-ray couch, thus saving patients from having to endure a hard, cold surface when being X-rayed,

For further information write or telephone.

HINDERS-LESLIES LIMITED
Higham Hill Road · London · E17 6EJ
Telephone: 01-531 7172 (10 lines) plus Ansafone

progress
through
research

S&N Member of the SMITH & NEPHEW Group of Companies

NORTH WEST THAMES AREA
HEALTH AUTHORITY with
ACTON TECHNICAL COLLEGE

Hospital Radiation Safety
A short course open to personnel working with ionising radiations. Starting with basic physics the course progresses to consider safety in detail. Course should be of interest to current and prospective Safety Officers or to those with a responsibility for safety.
Wednesdays 2–4 p.m. starting October. Fee £18

Computing for Radiographers and other Hospital Staff
A ten-week evening course commencing Wednesday, October 4th. General appreciation of computers, simple programming in Basic. Fee £15.

Computers in the Hospital Service
An eight-week evening course commencing in the new year. Detailed consideration of specific applications of computers in hospitals. Fee £15.

Ultrasound
A short course planned to start after Christmas to consider the basic physics of Ultrasound together with limited practical applications.

**DETAILS, APPLICATION FORMS, FROM
M. GRIMSHAW,
APPLIED SCIENCE SECTION,
ACTON TECHNICAL COLLEGE,
HIGH STREET, ACTON,
LONDON W3 6RD
Tel. 01-993 2344 ext. 2373/2129**

WANTED

DIAGNOSTIC RADIOLOGIST

required for group in large western Canadian city. Training in ultrasound, mammography and Nuclear Medicine an asset. Private clinic practice and hospital affiliation. Please reply to Box No. 7, British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Institute of Child Health – Hospital for Sick Children – London.

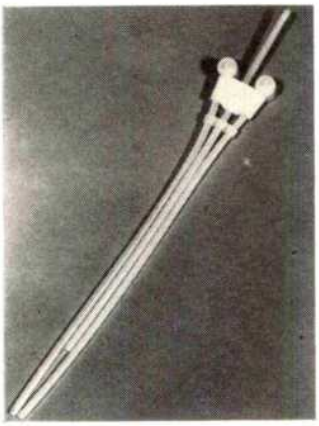
Paediatric Radiology
26th—27th October 1978

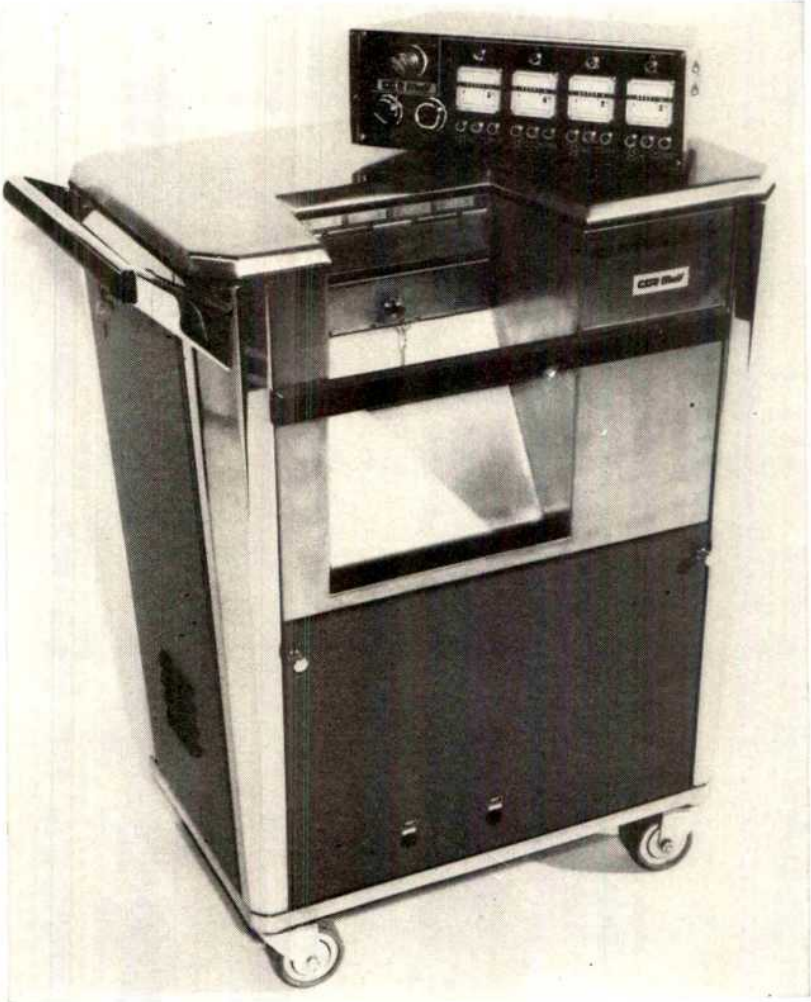
The Autumn 2 day refresher course in paediatric diagnostic imaging will be held in London. Further details and application forms are available from : The Secretary, Department of Paediatric Radiology, The Hospital for Sick Children, Great Ormond Street, London, W.C.1.

A safe easily movable after-loader for intracavity therapy

Above:
Transit Container L.4

Below:
Delouche Pattern Applicator





The Curietron is a versatile radioactive source after-loader designed for gynaecological intracavity therapy, eliminating radiation hazards to staff.

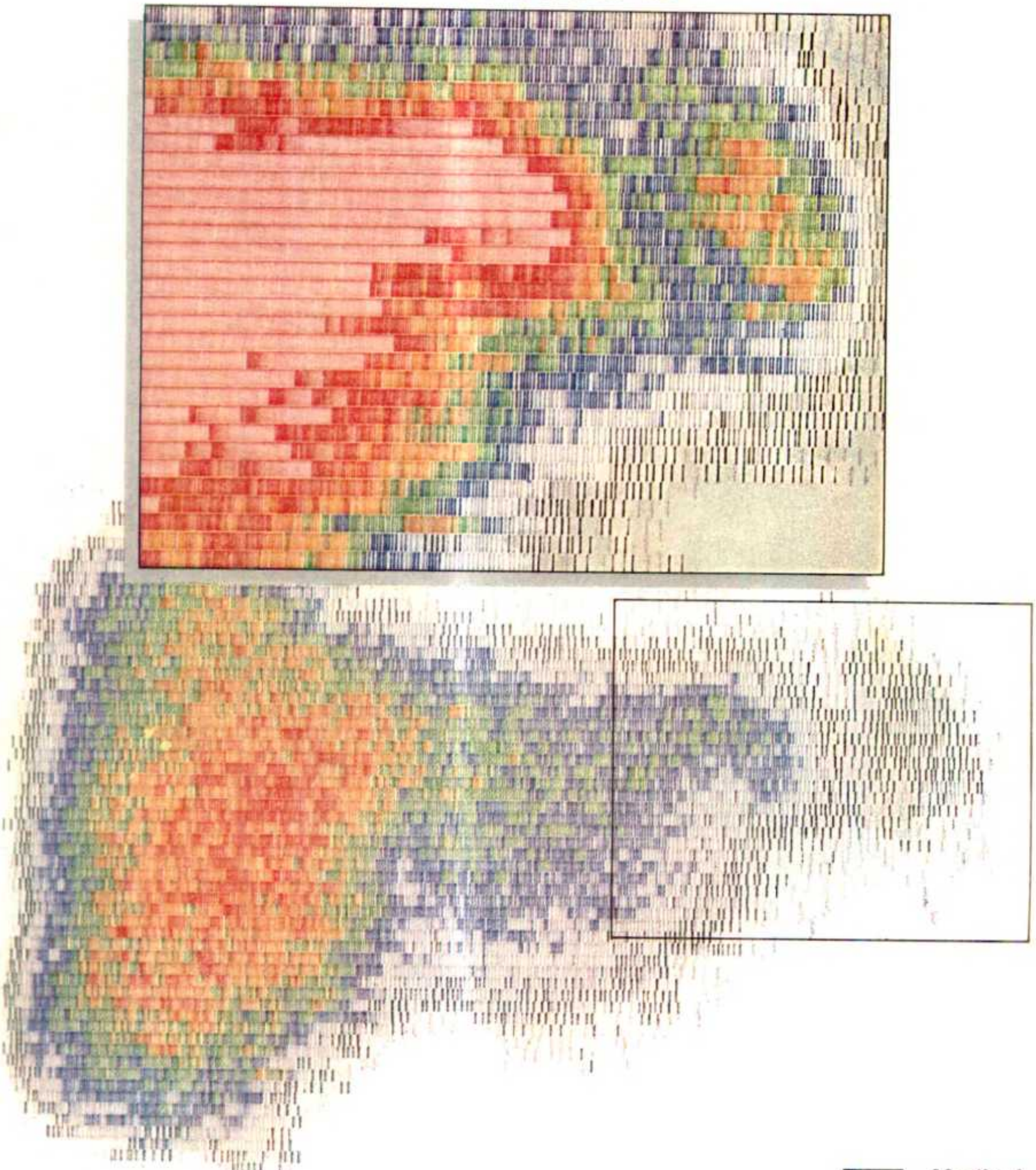
The size and weight of the Curietron are such that it can be easily moved by the operator. Remote control ejection and withdrawal of Caesium 137 sources is achieved through flexible tubes to the vaginal applicator and/or uterine probe with a control panel which indicates the positioning and the effective irradiation time.

CURIETRON
from

CGR

Full details and specifications from
CGR MEDICAL LIMITED
Astronaut House, Feltham, Middx. Tel: 01-890 8166

Rapid
evidence



PHILIPS

Medical
Systems

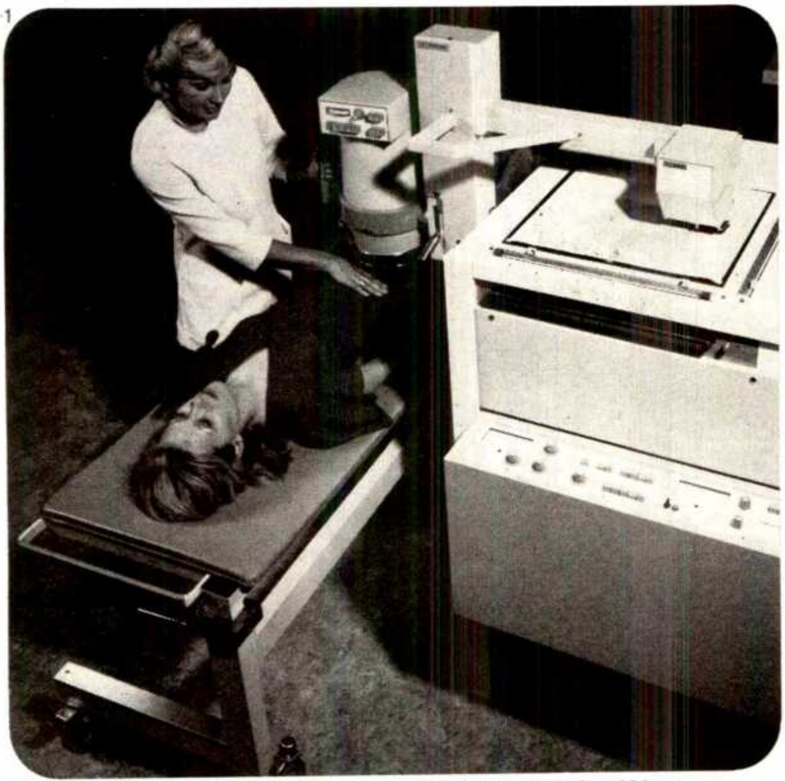
The lower of the two scintigrams shown here is a 42 x 42 cm liver scan. The other is a detail of that scan, reproduced to the same field size and with enhanced contrast to reveal otherwise indiscernable evidence of the spleen. Rapidly. Both scintigrams were made on a Philips Universal Scintillation Scanner.

The ability to reproduce comparable scans of total organs, with optimum contrast for regions of interest and without the necessity for time-consuming operational adjustment, is a unique feature of the Philips scintillation scanner.

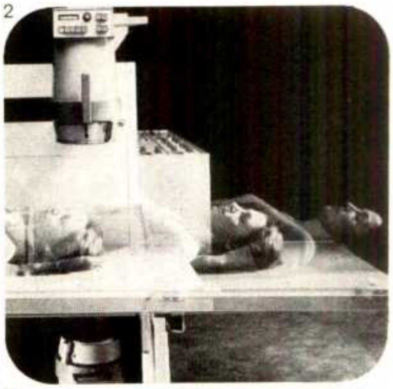
The existence of the scanner is still opportune because of its unsurpassed scanning results with high energy isotopes.

Here's how:

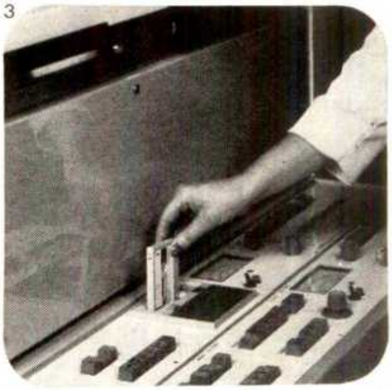
1



2



3



1 **The basic unit** comprises a 5 in. overtable detector, its 2 in. crystal thickness allowing a high counting efficiency also for high energies.
Ten preselected nuclide settings are provided as well as line interval selection and colour printer and photo scan adjustment and metering. A light beam pointer in the collimator enables the central axis to be accurately positioned. Scanning speed adjustment is continuously variable up to 75mm/s (450 cm/min or approx. 3in./s). All control functions are optimised and strategically positioned to ensure an exceptionally high degree of operational efficiency and safety.

2 **Total body and profile scanning** can also be performed by means of an optional motor-driven tabletop. This enables two-speed longitudinal movement of 100mm/min (approx. 4in./min) and 200mm/min (approx. 8in./min) and facilitates profile scanning using slit collimators. With the total body version the scanning area is 400 x 1600mm (15¾in. x 63in.); scintigram reduction factor being 4:1.
An optional under-table measuring head can be added which, together with a scan control unit, enables pulse sum scanning and $\beta+$ coincidence scans to be obtained.

3 **A second colour printer and photo scan unit** considerably extends the versatility of the Philips Universal Scintillation Scanner by enabling other original scans, based on different parameters, to be obtained. Furthermore, recording and storage of original scanning data can be achieved by means of a four track compact-cassette recorder. In the playback mode recordings can be reproduced using different scanner settings, i.e. different colour printer control signals.

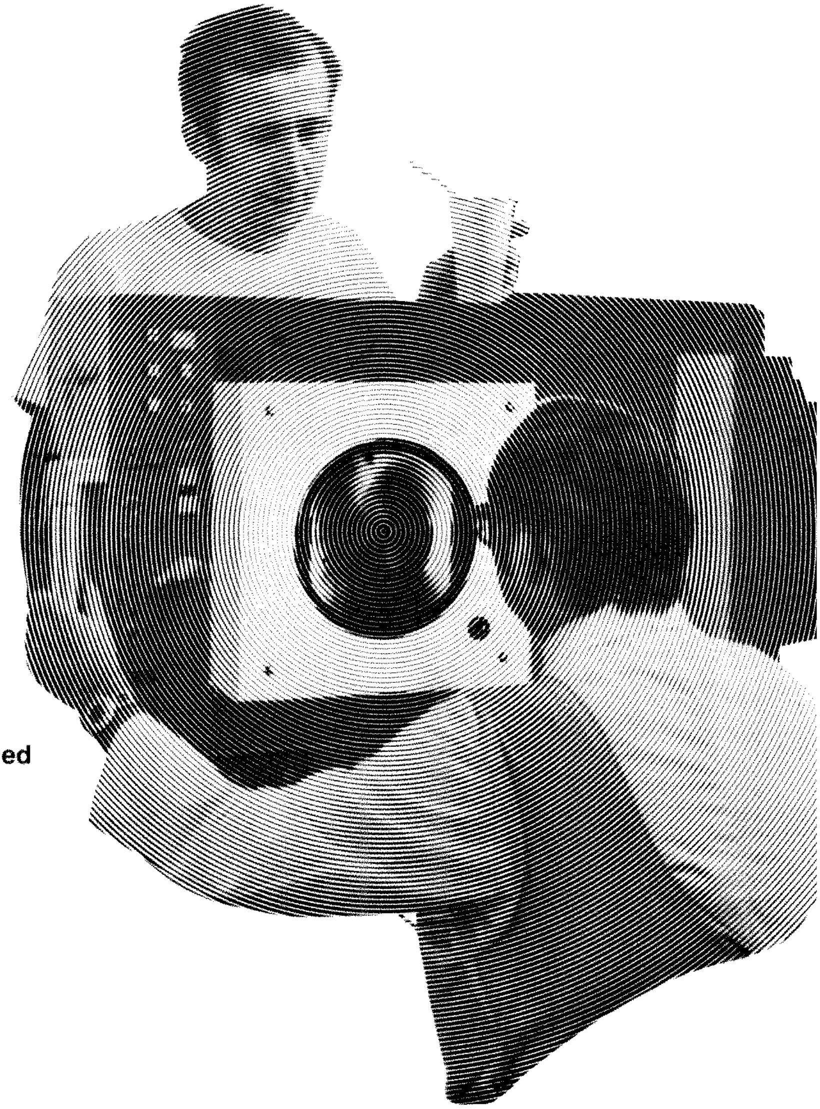
Part of a complete programme of nuclear medicine equipment and systems, and fully supported by an international service organisation, the Philips Universal Scintillation Scanner represents the perfect integration of operational simplicity and efficiency with applicational flexibility and reliability.

COUPON If you would like further evidence on Philips Universal Scintillation Scanner, or on any other equipment in our nuclear medicine programme, complete the coupon and send to: Philips Industries Medical Systems Division, Building QM, Room 326, Eindhoven, The Netherlands

Company: ____________________
Name/Position: ____________________
City/Country: ____________________
Street/P.O. Box: ____________________

Philips Medical Systems A Division of Philips Electronic and Associated
Industries Ltd. 45, Nightingale Lane, London SW12 8SX.

PHILIPS



40 years of
experience and
expert
knowledge
can be made
yours
very easily

Oldelft

Oldelft England ltd.
16 Barclay Road, Croydon CRO 1 JN
Tel. (01)681 1171, telex 946154

Odelscope: image-intensifier-improved fluoroscopy

Adding the Odelscope to your fluoroscopic device is combining fluoroscopic screen convenience with the benefits of image intensification in a simple and effective way. The excellent image definition, the low lag, the wide-angle screen and the easy compatibility of the Odelscope with practically all fluoroscopic tables give a new dimension to fluoroscopy.

Radiodiagnosis
Odelca x-ray cameras
100 mm System for spotfilm photography
Deltorax chest film changer
Odelscope image intensifier for fluoroscopy

Ultrasound
Real time linear phased array systems
Cardiac phased array sector scanners
General purpose gray-scale compound scanners

Nuclear medicine
Gamma cameras with complete range of accessories (e.g. multi-imager, whole body scanning bed)

Radiotherapy
4 and 15 MeV linear accelerators
Cobalt units

Radiotherapy planning
Simulix-Y simulator with Simtomix accessory for analog whole body tomography

Pulmonary function testing
Computerized equipment for the pulmonary lab
Automated procedures in spirometry, flow/volume loop analysis and exercise testing

Head Office: Holland, nv Optische Industrie De Oude Delft, 2612 xe Delft, Postbox 72, Tel (015) 13 29 23, 12 40 44, Telex 32 384
België/Belgique 2100 Deurne, Twee Gezusterslaan 34.
Tel (031) 24 93 05

Deutschland D 6300 Giessen (Lahn) Postfach 5420
Tel (0641) 4 10 49
España Madrid 16, Uruguay 13, Tel (01) 259 1695
France 91403 Orsay, B.P. 86, Tel (01) 907 5900
Italia 00146 Roma, Via della Vasca Navale 84, Tel (06) 55 84 311

Japan Osaka, Postbox 1042, Tel (06) 309 09 61
Sverige 17206 Sundbyberg 6, Postbox 670, Tel (08) 98 38 95
Schweiz 8618 Oetwil am See, Zelgistrasse 5, Tel (01) 92 91 316
USA Fairfax, Virginia 22030, 2735 Dorr Avenue
Tel (703) 573 7020

Five-star* economy

Created specifically to meet curre
demands for an economical but
versatile universal diagnostic
system, the DIAGNOST 54 offers
90/15° tilting table together with
many refinements generally
associated with only the most
sophisticated equipment:

- * integrated image intensifier system for optimum geometry
- * full counterbalancing, with no cumbersome ceiling suspension
- * universal serial changer program providing all subdivisions for gall bladder, oesophagus and arthrography
- * Anatomically Programmed Radiography for selecting your chosen exposure parameters at the touch of a button
- * automatic beam collimation to the cassette format in use

The five-star DIAGNOST 54: only its price is economy class.

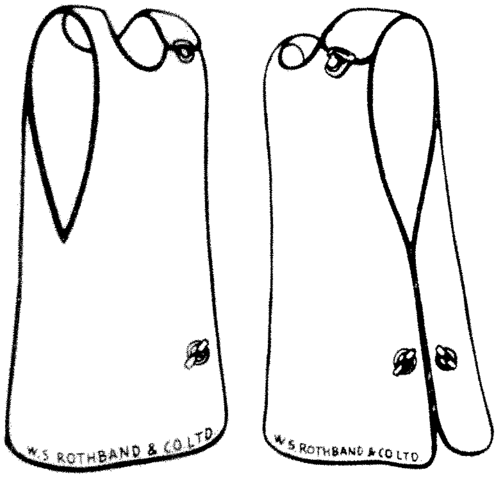
PHILIPS

PHILIPS

Medic
Syster

DOCTOR "C" TYPE DOUBLE-SIDED APRON

Right side closed, left side has push-in-clip shoulder fastening,
(or if "Velcro" preferred, please state on order).



Super-flexible–Multi-layered.

Foam padded shoulders.

Standard size is 24 in (61 cm) wide. Ladies slim fitting 21 in (53 cm) also available.

Lengths, choice of 33 in (84 cm), 36 in (91 cm), 39 in (99 cm), 42 in (107 cm).

Washable PVC colours, choice of royal blue, white, green, yellow, red.

Lead equivalents, choice of 0.25 mm, 0.35 mm, 0.50 mm.

This Apron has been specially designed by our Company for operators who stand "right-side-on" and who require protection without a gap on the right hand side.

W. S. ROTHBAND & CO. LTD
Telephone 061–834 1303

21 Elizabeth Street
Manchester M8 8WT, England

Established 1860

Waikato Hospital Board

Director of Department of Diagnostic Radiology

Waikato Hospital, Hamilton, New Zealand

This post becomes vacant on 1 October 1978, and to fill it, applications are called for from medical graduates with pertinent postgraduate qualifications. The Director is not only concerned with the overall supervision of the Waikato Hospital Board in the development of diagnostic imaging services over the whole Board's area. There are five other hospitals throughout its area involved in the provision of such services. It is intended that the position will be a full time one.

The Waikato Hospital has 912 active beds, and provides all standard and specialist clinical services. It also acts as a base hospital for a population of 250,000 people.

Encompassed in its area of service is a rich pastoral and agricultural area, and all facilities for education and summer and winter sports.

The X ray Department is a modern one, and includes an active Department of Diagnostic Ultrasound. The hospital also has a Department of Nuclear Medicine.

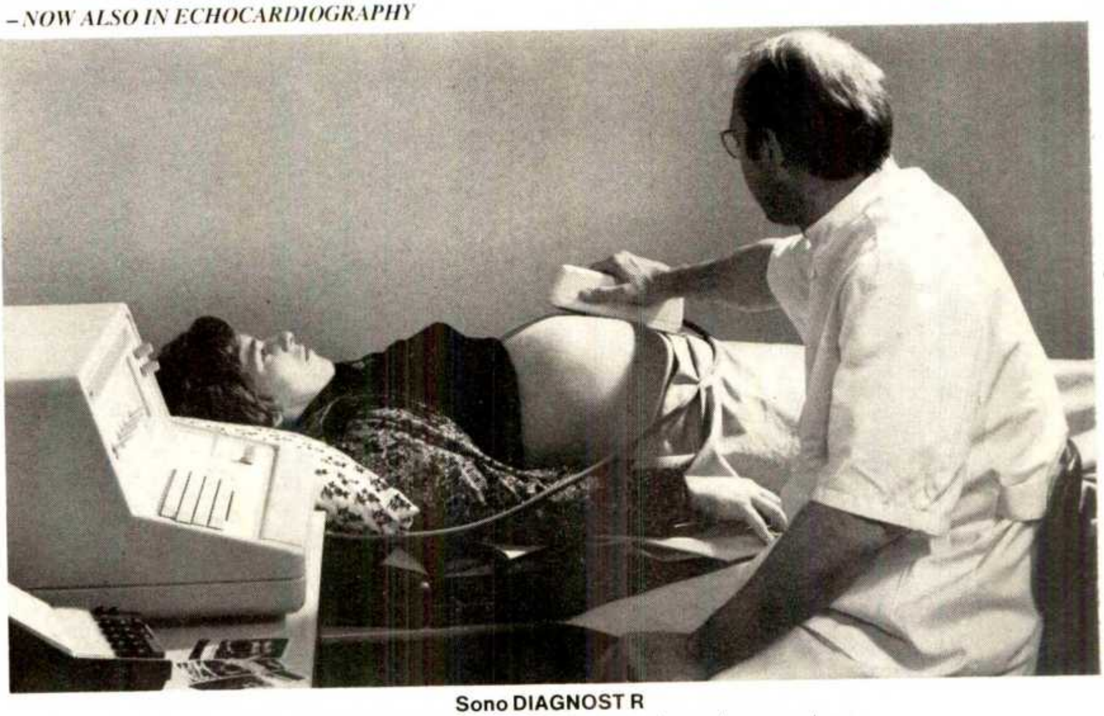
Two other full-time radiological positions are being currently advertised, and applicants could signify their willingness for their names to go forward for these if their applications for the Directorship were unsuccessful.

Salary will be in the range NZ$17,060–$22,161 plus $365 Cost of Living Order plus 3.5% Special Adjustment. The commencing salary within the scale will be set by the Medical Officers Salaries Grading Committee according to the qualifications and experience of the appointee.

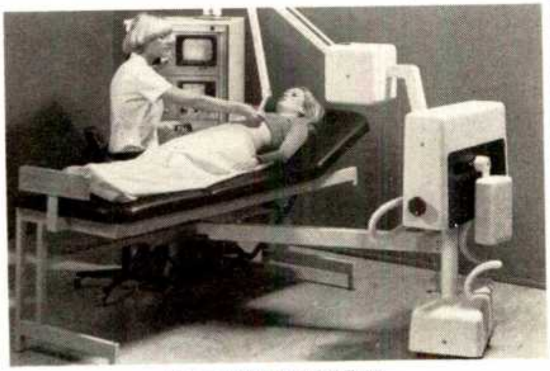
Further particulars are available from the Surgeon Superintendent, Waikato Hospital, Hamilton, New Zealand and application forms and conditions of appointment are available from the Chief Executive, Waikato Hospital Board, P.O. Box 934, Hamilton, New Zealand, with whom applications close on 1 September 1978.

The ultrasonic challenge accepted

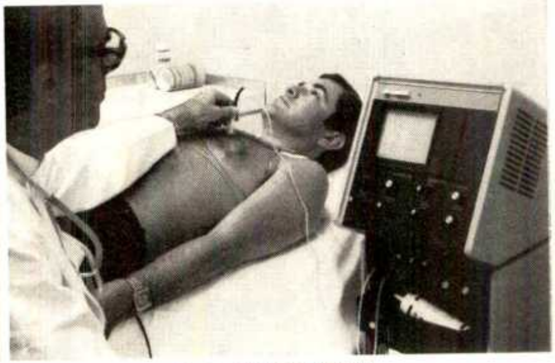
– NOW ALSO IN ECHOCARDIOGRAPHY



Sono DIAGNOST R
For real-time imaging particularly in obstetrics and gynaecology



Sono DIAGNOST B50
For tomographic imaging in B-mode, with A-mode
and M-mode facilities



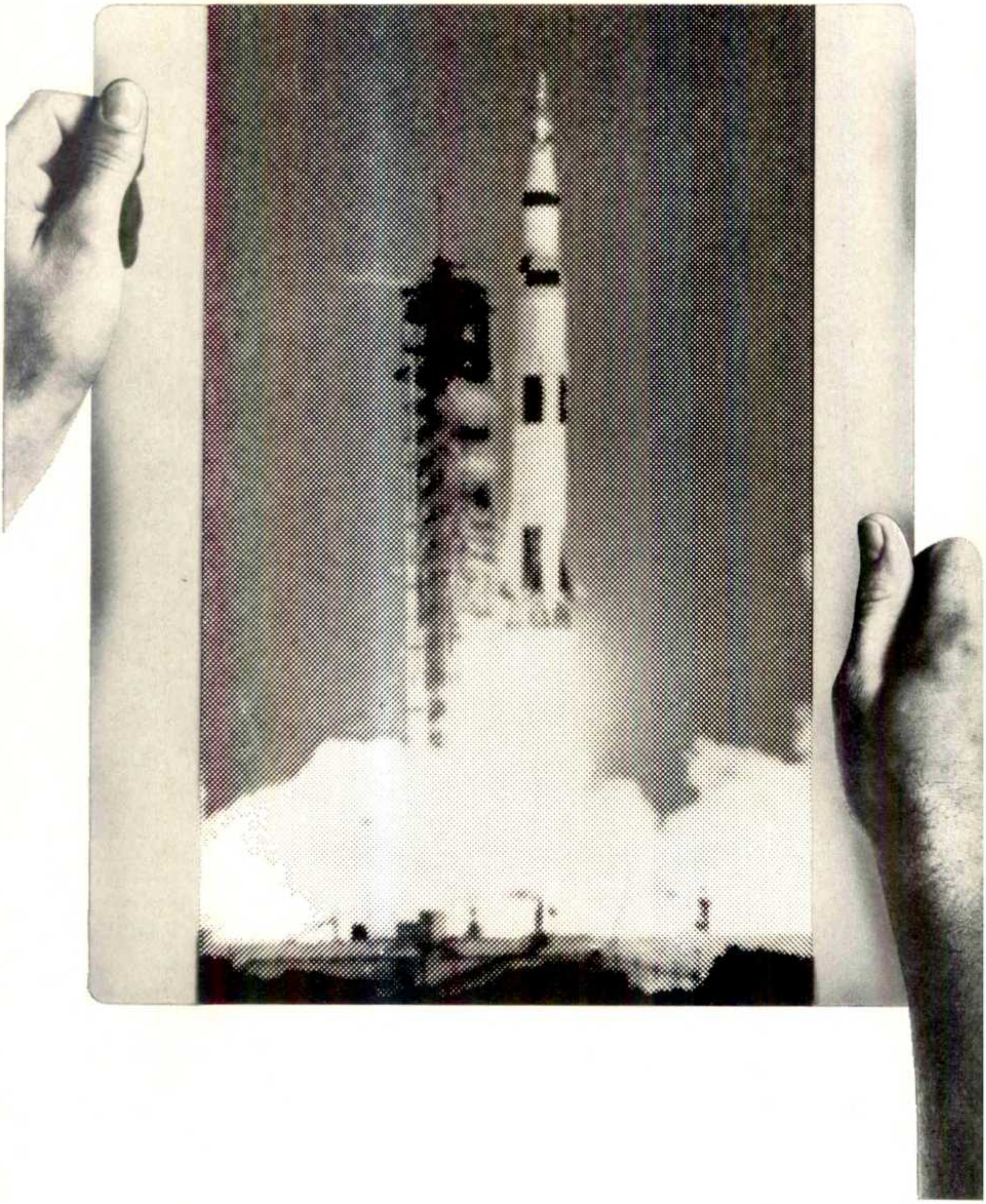
Sono DIAGNOST M
For echocardiography in T.P. mode

Sono DIAGNOST A (not illustrated)
For echo-encephalography in A-scan mode

For details please contact Philips Medical Systems, Ultrasonics Division,
45 Nightingale Lane, London SW12 8SX. Telephone: 01-673 7766.

PHILIPS

PHILIPS **Medical Systems**



ILFORD shows up everywhere.

The performance you expect – and get from ILFORD X-ray materials shows up in many other, sometimes unexpected places.

For if there's an image to be recorded, ILFORD will seldom be far away.

Our Microfilm products show up in the computer world recording output and in the fields of finance and industry with image retrieval systems. And again in the security recording of the massive weekly tide of football pool coupons.

We show up again in newspapers and magazines where ILFORD films and papers provide the illustrations which are often converted into print by ILFORD Graphic Arts materials.

Our Photographic products can show up everywhere from banks (Surveillance film for high security areas) to outer space (Nuclear emulsions as used in every U.S. space shot so far).

In Colour Printing too – amateur or professional – Cibachrome shows up wherever standards really count. You may not see the name, but you will see the results – everywhere.

It is this very involvement in so many fields that supports the broad fundamental research and keeps the ILFORD products you use efficient and up-to-date. One last thing from ILFORD that always 'shows up': the after sales and technical service.

ILFORD
X-RAY

ILFORD Limited, Basildon, Essex.

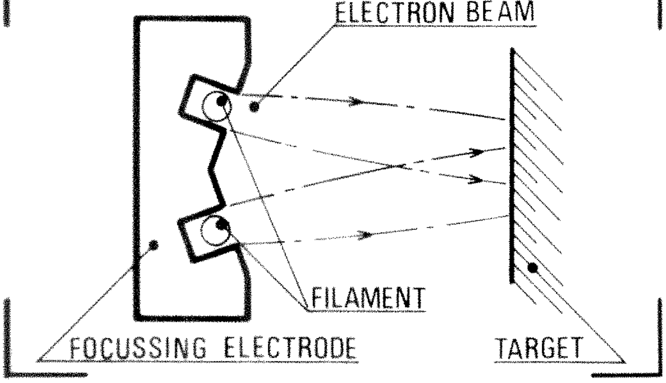
There's more
to ILFORD than meets
the eye

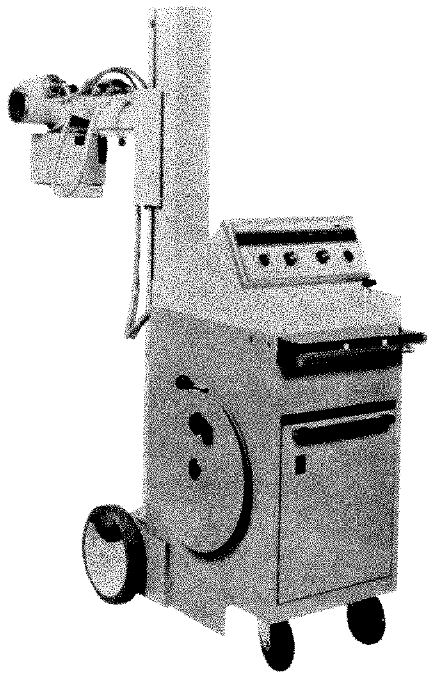
NEW second generation

600 mAp
Capacitor Discharge Mobile

- SUPER OUTPUT 600 mAp/125 kVp
- MILLISECOND SWITCHING 2–60 mAs in 15 steps
- IMPROVED MANOEUVRABILITY three forward speeds and two reverse – extra low speed for bedside adjustment
- UNIQUE HIGH POWER CD600 X-RAY TUBE fine focus, high capacity
- LOW COST half cost of cordless systems

NEW CD 600 X-RAY TUBE





The second generation series CD600 capacitor discharge X-ray tubes have been designed on a new principle using a focussing electrode to cut-off the tube current in place of the grid which was previously used.

With this tube, two 0·8 mm focal spots are superimposed on the target slightly shifted from each other. This results in a high power peak intensity distribution over a focal spot effective size 1·2×1·2 mm.

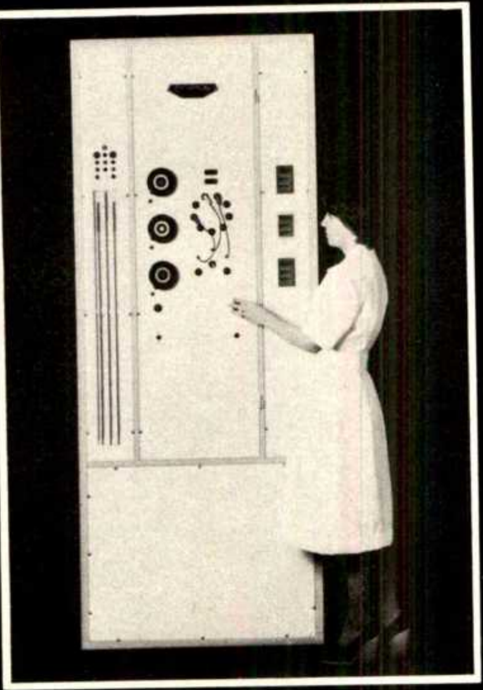
A great improvement is achieved in the Modulation Transfer Function over the conventional tube and therefore excellent detail at high tube mA loadings is achieved.

The use of this double focus combination also reduces individual filament temperature and provides longer tube filament life than conventional tube design.

Before making any decisions, contact us and arrange a demonstration in your own Department.

TODD RESEARCH LTD
ROBJOHNS ROAD
CHELMSFORD CMI 3DP
TEL. (0245) 62233/7 TELEX 99327

*Our 1978–9 catalogue is now available. Contact us and a copy will be mailed by return.

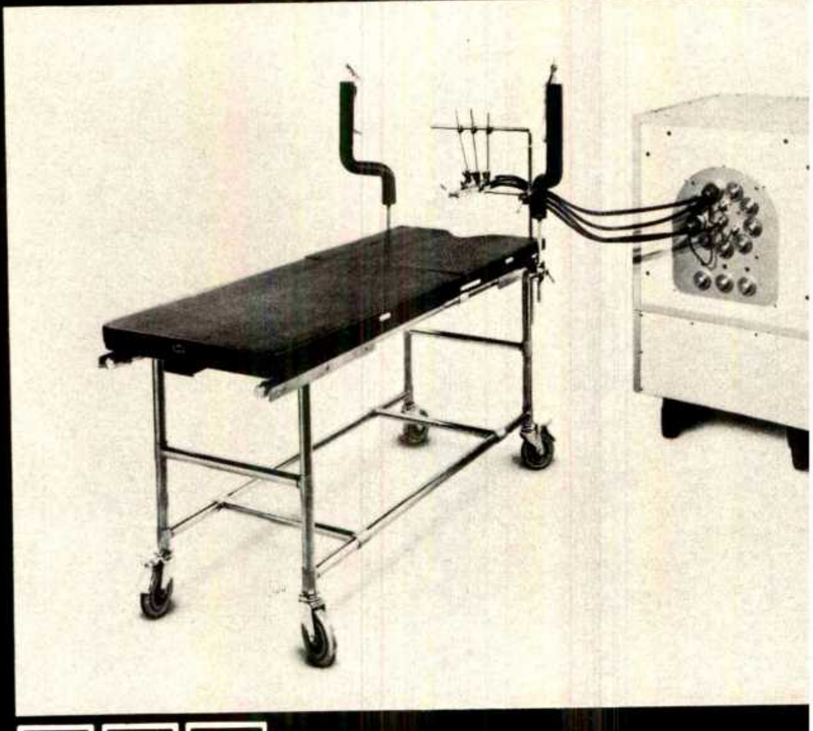


Cathetr
Remote loa
Intracavitar
using Coba

The Cathetron has now be
for over a decade and is us
30 hospitals in nearly 20 di

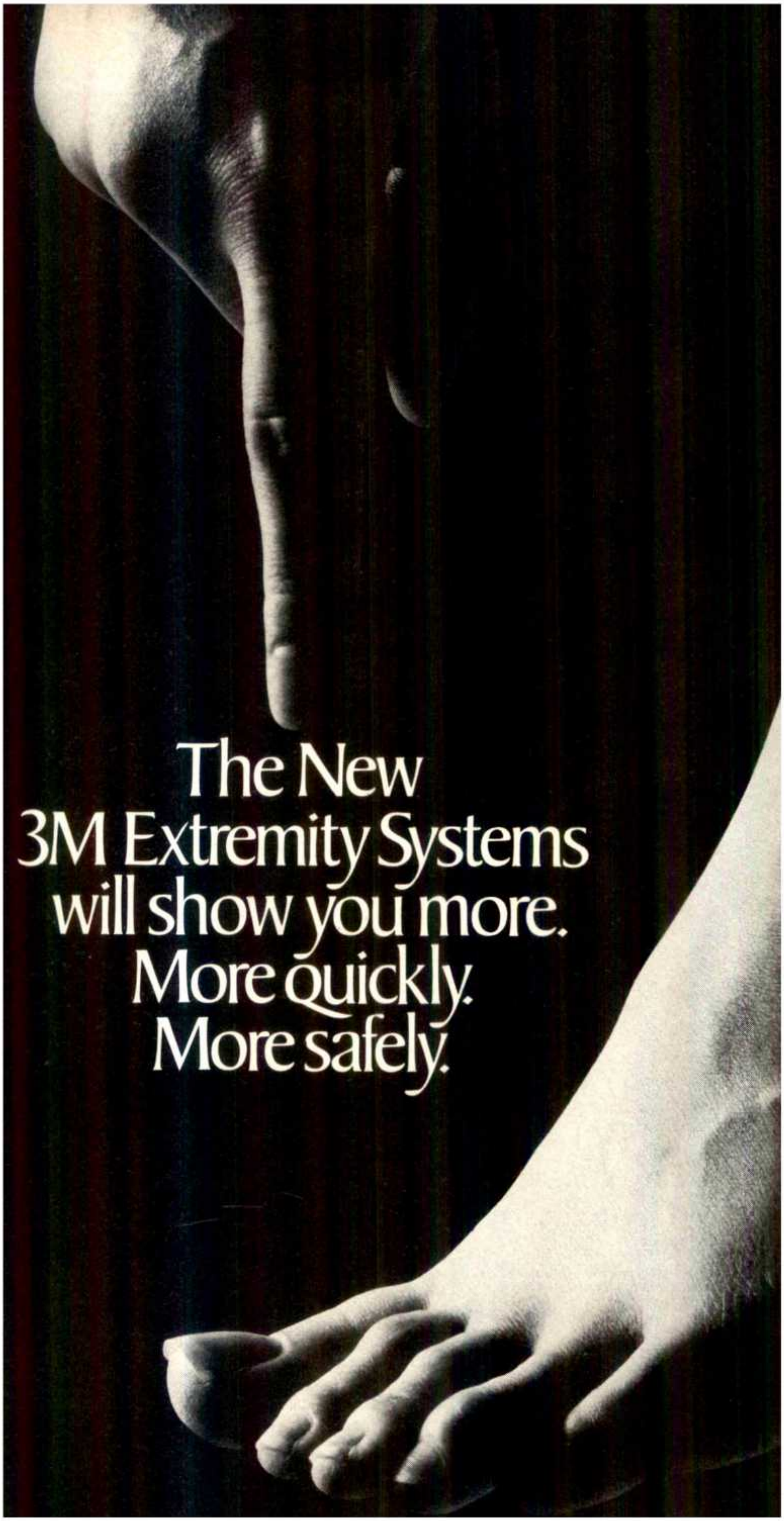
Use of the Cathetron gives
from radiation hazards, to
reduces treatment time to
ensuring that the Catheter
correct location. These sh
times mean that many pat
treated as out-patients an
not take up valuable bed s

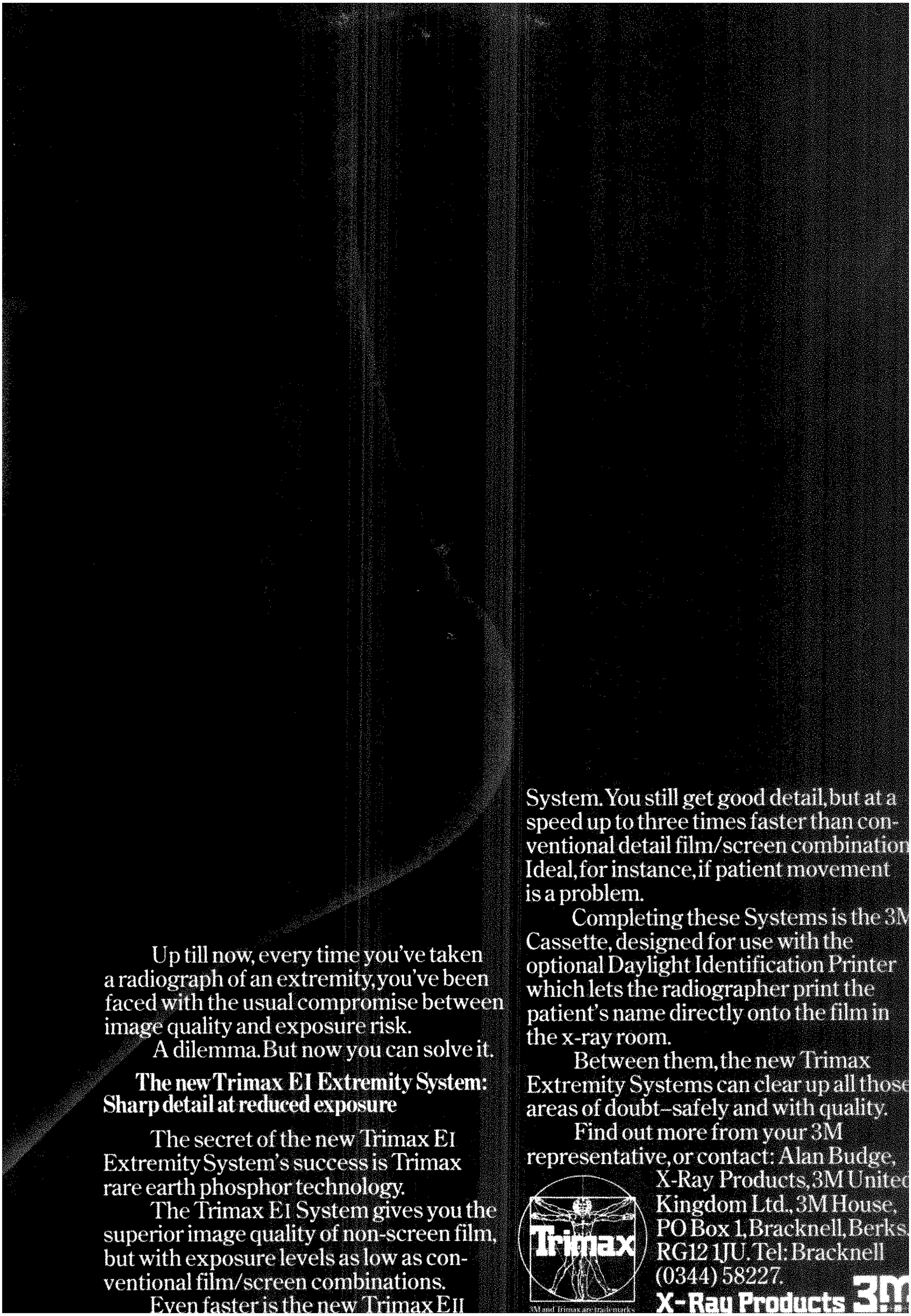
The Cathetron is used for
treatments; treatments of
and bronchi as well as gyn
cases.



TEM Instruments Limit

Gatwick Road, Crawley, Sussex, RH10 2RG, England Tel 0293 312
Telex 87397, Grams TESTMENT CRAWLEY


The New
3M Extremity Systems
will show you more.
More quickly.
More safely.



Up till now, every time you've taken a radiograph of an extremity, you've been faced with the usual compromise between image quality and exposure risk.

A dilemma. But now you can solve it.

The new Trimax E1 Extremity System: Sharp detail at reduced exposure

The secret of the new Trimax E1 Extremity System's success is Trimax rare earth phosphor technology.

The Trimax E1 System gives you the superior image quality of non-screen film, but with exposure levels as low as conventional film/screen combinations.

Even faster is the new Trimax EII System. You still get good detail, but at a speed up to three times faster than conventional detail film/screen combinatio Ideal, for instance, if patient movement is a problem.

Completing these Systems is the 3 Cassette, designed for use with the optional Daylight Identification Printer which lets the radiographer print the patient's name directly onto the film in the x-ray room.

Between them, the new Trimax Extremity Systems can clear up all thos areas of doubt–safely and with quality.

Find out more from your 3M representative, or contact: Alan Budge,
X-Ray Products, 3M Unite
Kingdom Ltd., 3M House,
PO Box 1, Bracknell, Berks.
RG12 1JU. Tel: Bracknell
(0344) 58227.

Trimax

3M and Trimax are trademarks

X-Ray Products

SIEMENS

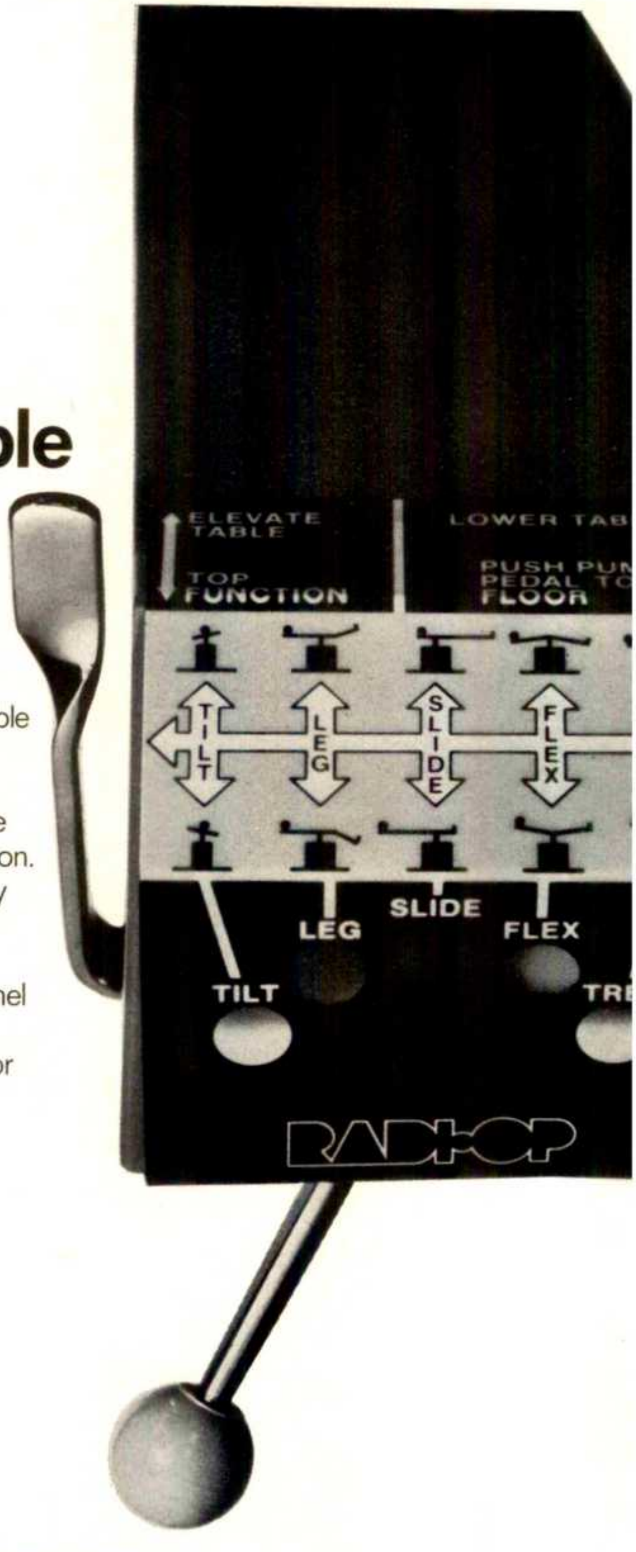
An advanced mobile surgical table with just two simple controls

Siemens Radi-op – a universal table with movable top. The single movable control arm and a simple toe-pedal operation gives complete mobility. The control arm smoothly positions the table to any of the six basic settings – quickly and with error-free selection.

This variety of precise positions helps make any operating procedure smoother, speedier and more efficient.

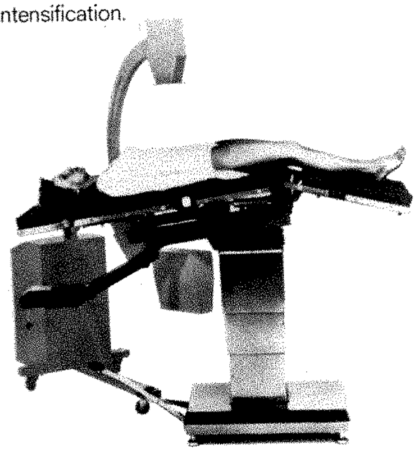
Other features include a built-in cassette channel for standard radiology procedures, a completely sealed fluid drive hydraulic system and a positive floor lock system – plus a range of accessories.

For full details write to: Siemens Limited,
Medical Group, Siemens House, Windmill Road,
Sunbury-on-Thames, Middlesex, TW16 7HS.
Tel: 09327 85691

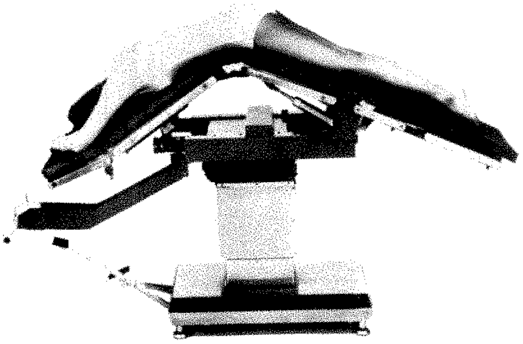


In the world of electro-medicine Siemens has the answer

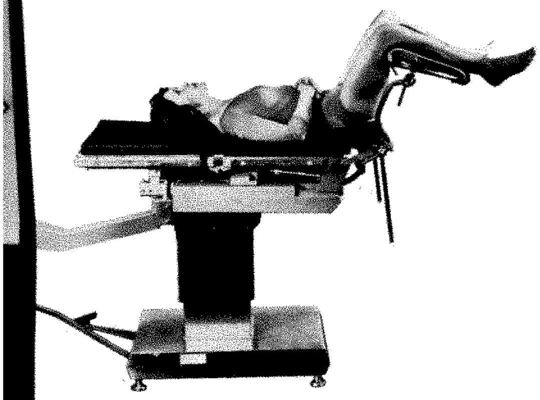
Gall Bladder. Unobstructed access above and below the table top for use with image intensification.



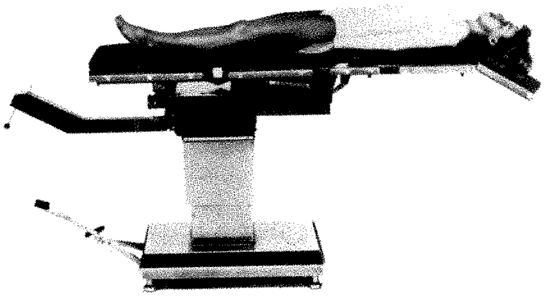
Proctology. Flex control provides smooth, effortless positioning of the patient for proctologic procedures.



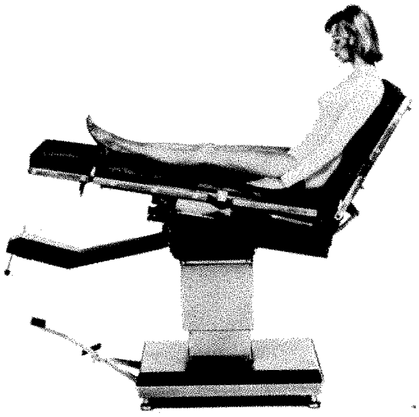
Lithotomy. The Radi-op table offers elevation of the pelvic area to provide access to the surgical site.



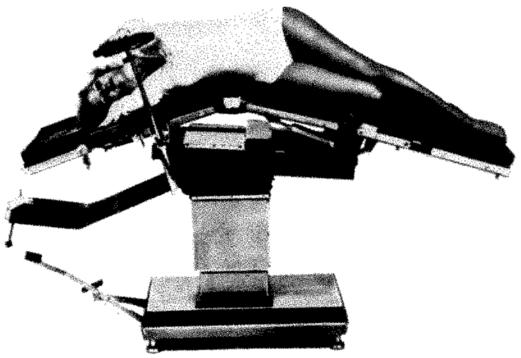
ENT. Total unobstructed access to the patient by the surgical team.

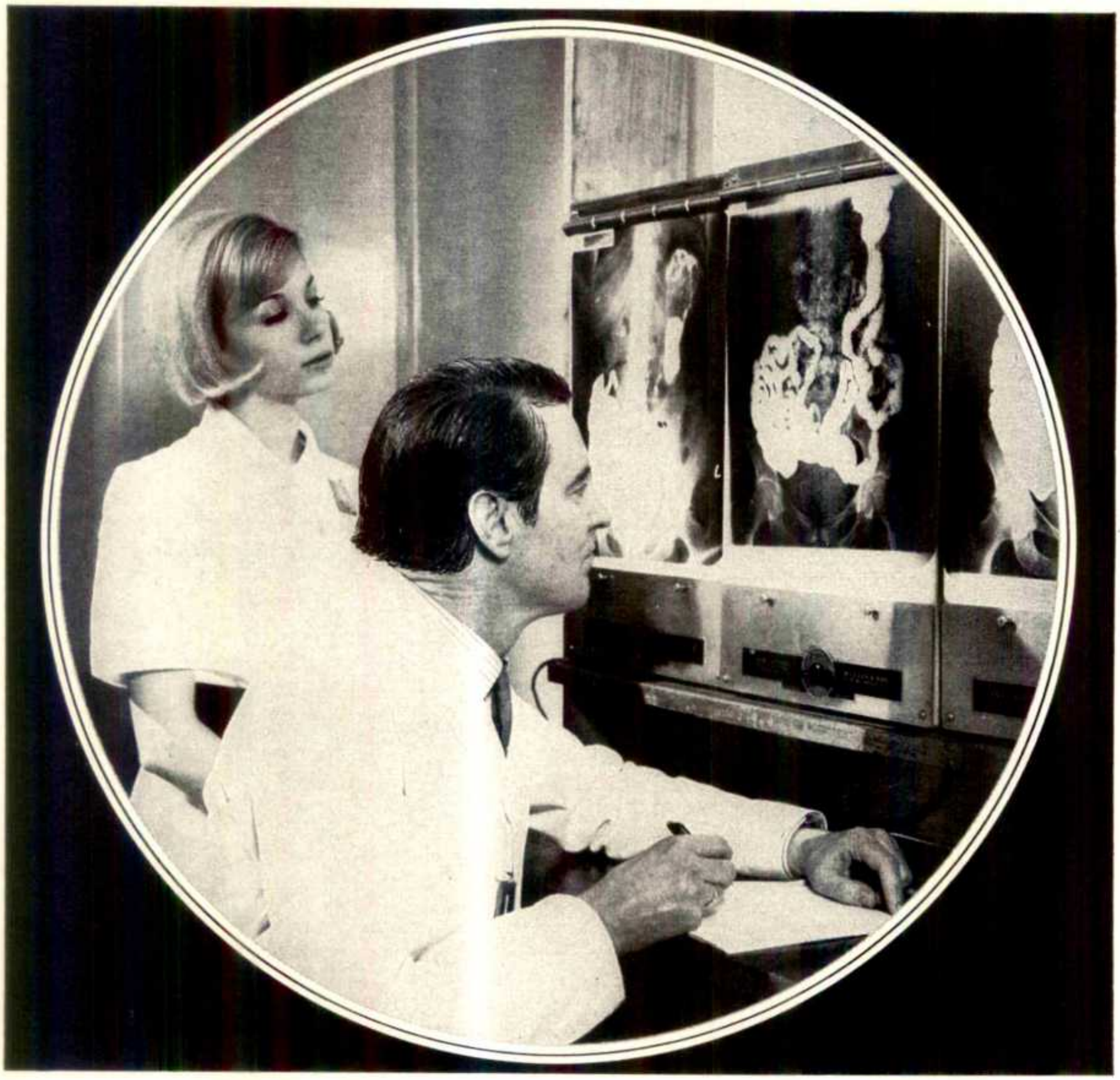


Neurosurgery. Unimpeded approach by the surgical team for all neurosurgical procedures performed in the sitting position.



Kidney. Optimum table flex without use of a kidney elevator for greater patient safety and comfort.





True qualities that come as a revelation

Conray contrast media

The dependable qualities and wide scope of 'Conray' contrast media have been clearly demonstrated throughout many years of use in the field of radiodiagnosis. 'Conray' offers a choice of formulations designed to provide wide margins of safety and comfort for the patient together with optimum visualization in a comprehensive range of procedures and techniques.

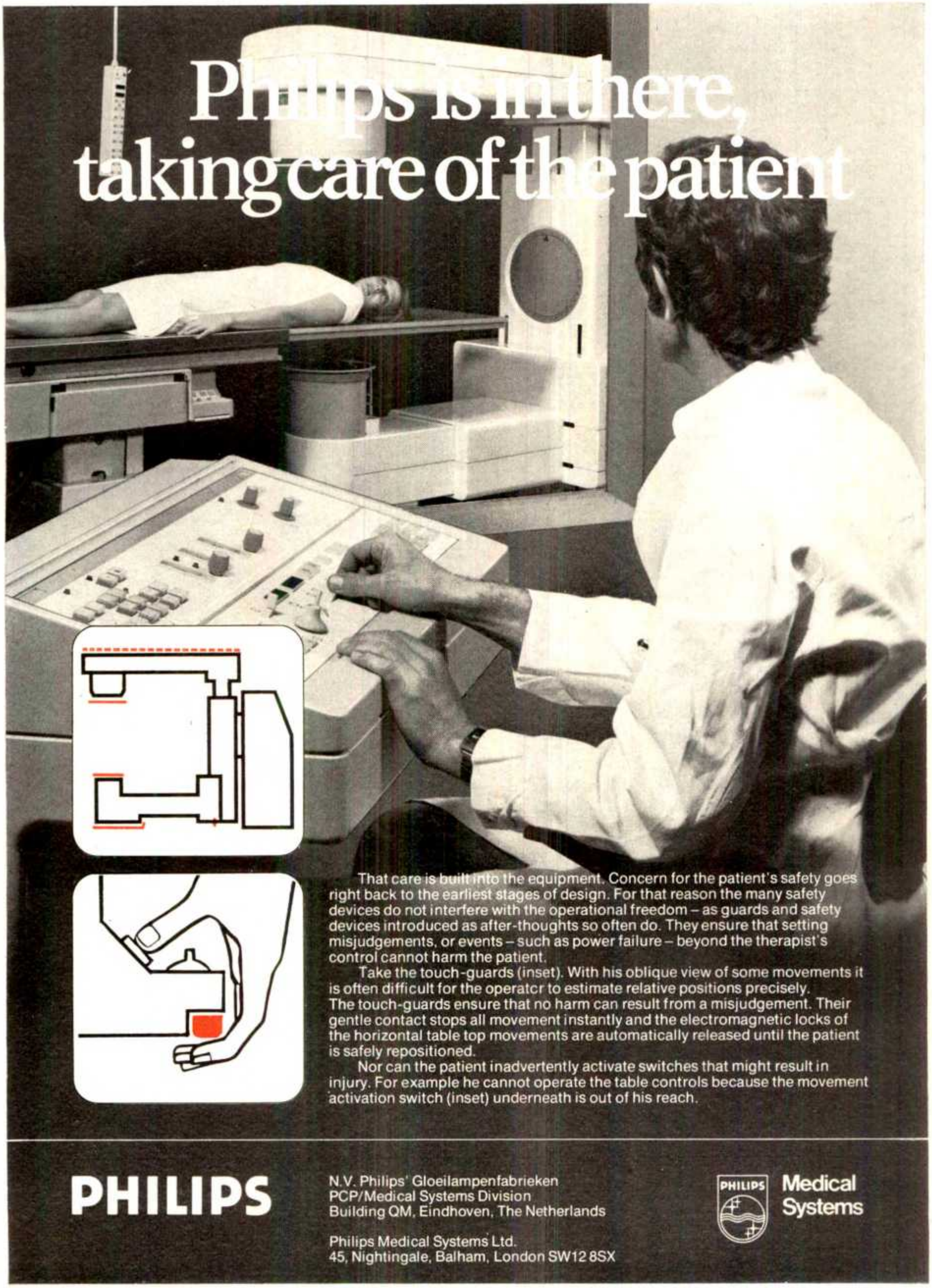
'Conray'* contrast media are formulations of meglumine iothalamate, sodium iothalamate or combinations of the two.

*trade mark of Mallinckrodt Inc.
Further information is available in the data sheet
May & Baker Ltd Dagenham Essex RM10 7XS

M&B May&Baker

A member of
the Rhône-Poulenc
Group of Companies

MA 6335



Philips is in there, taking care of the patient

That care is built into the equipment. Concern for the patient's safety goes right back to the earliest stages of design. For that reason the many safety devices do not interfere with the operational freedom – as guards and safety devices introduced as after-thoughts so often do. They ensure that setting misjudgements, or events – such as power failure – beyond the therapist's control cannot harm the patient.

Take the touch-guards (inset). With his oblique view of some movements it is often difficult for the operator to estimate relative positions precisely. The touch-guards ensure that no harm can result from a misjudgement. Their gentle contact stops all movement instantly and the electromagnetic locks of the horizontal table top movements are automatically released until the patient is safely repositioned.

Nor can the patient inadvertently activate switches that might result in injury. For example he cannot operate the table controls because the movement activation switch (inset) underneath is out of his reach.

PHILIPS

N.V. Philips' Gloeilampenfabrieken
PCP/Medical Systems Division
Building QM, Eindhoven, The Netherlands

Philips Medical Systems Ltd.
45, Nightingale, Balham, London SW12 8SX

PHILIPS **Medical Systems**

**ST. MARK'S HOSPITAL
FOR DISEASES OF
THE COLON & RECTUM**
City Road, London EC1V 2PS

**RADIOLOGY IN COLITIS
AND
COLORECTAL NEOPLASIA**

Day Course on TUESDAY, 24th OCTOBER 1978.

Fee £5 including lunch and refreshments.

For further details apply to:
Dean's Secretary,
St. Mark's Hospital,
City Road, London EC1V 2PS

**Dartford and
Gravesham
Health District**
West Hill Hospital

**Basic-Grade
Radiologist**

required for a busy department with work in both the main and Ultra Sound Departments. Some experience in Ultra Sound would be an advantage but not essential.
West Hill Hospital is situated in the heart of Dartford close to all local amenities and transport and within easy reach of London and the Kent Coast.

Applications please in writing giving full details and the names and addresses of two referees to Sector Administrator, West Hill Hospital, Dartford, Kent.

The British Journal of Radiology
REVIEW ARTICLES

The Possibility of Hazard in Medical and Industrial Applications of Ultrasound, by C. R. Hill (August 1968)	50p
An Evaluation of Conventional Radiography in Acquired Heart Disease, by R. G. Grainger (October 1970)	50p
The Plain Chest Radiograph in Congenital Heart Disease, by K. Jefferson (November 1970)	70p
The Kinetics of Tumour Cell Proliferation and Radiotherapy, by M. Tubiana (May 1971)	75p
Radiation Therapy in Diseases of Larynx, by R. Morrison (July 1971)	75p
The Radiological Diagnosis of Adrenal Tumours, by D. Sutton (April 1975)	75p
Bone Scanning, by M. V. Merrick (May 1975)	75p
Tumour Imaging Radiopharmaceuticals, by A. H. F. Paterson and V. R. McCready (July 1975)	50p
The potential of Californium-252 in Radiotherapy, by E. J. Hall and H. Rossi (October 1975)	75p
Craniopharyngioma: based on 160 cases, by M. Banna (March 1976)	80p
Pancreatic Scanning, by J. E. Agnew, M. Maze and C. J. Mitchell (December 1976)	70p
Gastro-oesophageal Reflux, Hiatus Hernia and the Radiologist, with Special Reference to Children, by G. M. Steiner (March 1977)	65p
Classification and radiographic features of uterine malformations: hysterosalpingographic study, by E. Zanetti, Liliana Recanatini Ferrari and G. Rossi (March 1978)	55p
The sensitivity of the human breast to cancer induction by ionizing radiation, by R. H. Mole (June 1978)	60p

Available from the Publications Office, British Institute of Radiology, 32 Welbeck Street, London, W1M 7PG (remittance with orders less than £1, please).

AXISCAN 5

The new portable real-time ultrasound scanner from Kontron Roche

• Built to a unique design, offering all the facilities you require for obstetric and general abdominal scanning • Truly portable design makes it very easy to use in ante-natal clinics and other departments within hospitals • Simple operation facilitates routine obstetric investigations with the minimum of fuss • Fetal maturity estimations can be established quickly using the integral electronic calipers which automatically reproduce an on-screen digital display. • Results are permanently recorded with the built-in camera. • The excellent grey-scale display shows moving structures up to 25 cm deep. • All our customers are backed by a national 24 hour Kontron Roche service.

KONTRON ROCHE

serving hospitals throughout the world

For further information, please complete the coupon below and post to Dr. Hargreaves, Kontron Instruments Ltd., P.O. Box 188, Watford WD2 4YX or telephone Watford (0923) 47666

Please contact me to arrange a demonstration of/send me further information about/ the Axiscan 5.

NAME. . . . .

POSITION . . . .

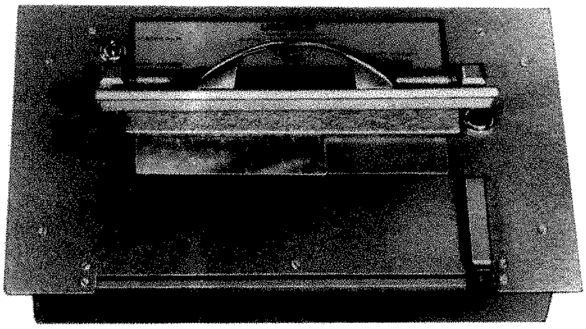
ADDRESS. . . . .

. . . .

. . . .

TELEPHONE . . . .

UNIVEX



An automatic actinic film marker with maximum flexibility to meet individual preference: it combines great reliability with competitive price and sales have now substantially passed the thousand mark.

Standard window 2⅜ in. by 1 in.
(for use with standard lead masks and paper slips)
Special windows up to 6 in. by 1 in.
Deck size 10¾ in. by 7¼ in.
Height of deck 2 in.
Overall height 3¼ in.
Sliding bar film stop.
Overhanging deck for flush mounting; absolutely stable for surface use.

CUTHBERT ANDREWS
EVERYTHING X-RAY LTD.
5 HIGH STREET, BUSHEY VILLAGE, WATFORD WD2 1BE
Overseas telegrams: EXRAYZE WATFORD
Telephone: 01-950 2525

1978, *British Journal of Radiology*, *51*, 563–573

VOLUME 51 NUMBER 608 AUGUST 1978

The British Journal of Radiology

Computed tomography in spontaneous intracerebral haematomas

By B. E. Kendall, F.R.C.P., F.R.C.R., and E. W. Radue, M.D.

The National Hospital For Nervous Diseases, Queen Square, London, W.C.1

(*Received January, 1978 and in revised form March, 1978*)

ABSTRACT

The typical computed tomographic (CT) features of a recent intracerebral haematoma are a homogenous region of increased attenuation surrounded by a well demarcated relatively narrow low attenuation ring (LAR). The pathology of the LAR is controversial, but it corresponds well with a zone of ischaemic necrosis which is observed around most intracerebral haematomas examined at autopsy.

Observations are made on spontaneous intracerebral haematomas and on blood samples which confirm that extravasated blood clot undergoes a variable degree of retraction which is completed within six hours. This suggests that the LAR in recent haematoma is due to damage caused by the greater volume of the precontracted haemorrhage on the surrounding brain.

CT abnormalities in intracerebral haematomas were studied; features which were useful in distinguishing spontaneous haematomas and those which affected prognosis are discussed.

The computed tomographic (CT) features of intracerebral haemorrhage have been documented and most of the appearances have been explained. The contribution of the various constituents of blood to its attenuation on CT have been established (New and Aranow, 1976, Norman *et al.*, 1977). Differences between attenuation of blood samples are mainly due to variations in haemoglobin content and reflects the degree of anaemia or polycythaemia. Attenuation is unchanged by clotting, until contraction takes place; with contraction of clot, fluid is expelled from it, haemoglobin concentration rises within it and attenuation increases. The degree of contraction varies but it can be estimated from attenuation measurements made entirely within the contracted clot and the circulating haemoglobin at the site of bleeding. The original volume of a recently contracted clot which is confined to cerebral substance can therefore be estimated from the final volume shown on CT. Since the well defined low attenuation zone around a haematoma is presumed to be within brain damaged by the haemorrhage, it was of interest to investigate any relationship between the size of this LAR and that of the original volume of a haemorrhage confined to brain substance.

Prognosis in spontaneous intracerebral haemorrhage is likely to be influenced by the position and size of the haematoma as well as by the rate of bleeding, its route of extension and other clinical and radiological features. We considered it to be worthwhile to correlate the influence of as many of these factors as possible in the same group of patients.

MATERIALS AND METHODS

Specimens of normal blood were scanned unclotted, immediately after clotting, again after three hours, six hours, 24 hours and three days (Fig. 1).

The clinical notes, CTs and angiograms of patients presenting with subarachnoid or intracerebral bleeding were reviewed. From this group of adequately investigated patients only those with intracerebral haematomas with no underlying local or systemic abnormality, apart from hypertension in some cases, were analysed further.

The age, sex and haemoglobin in the blood taken as closely as possible to the time of haemorrhage and the presence of hypertension (defined as blood pressure consistently above 160/100 mm Hg) were noted. The mean attenuation (mu) within the central part of the haematomas was measured by averaging the readings from 16–20 central pixels and the variation of mu with time in cases with follow-up scans was recorded. Extension of haemorrhage into the ventricular system was charted as confined to part of one lateral ventricle (Fig. 2) or the third ventricle, in which case at least one of the lateral ventricles and usually the fourth ventricle also contained blood (Fig. 3) or involving both lateral ventricles.

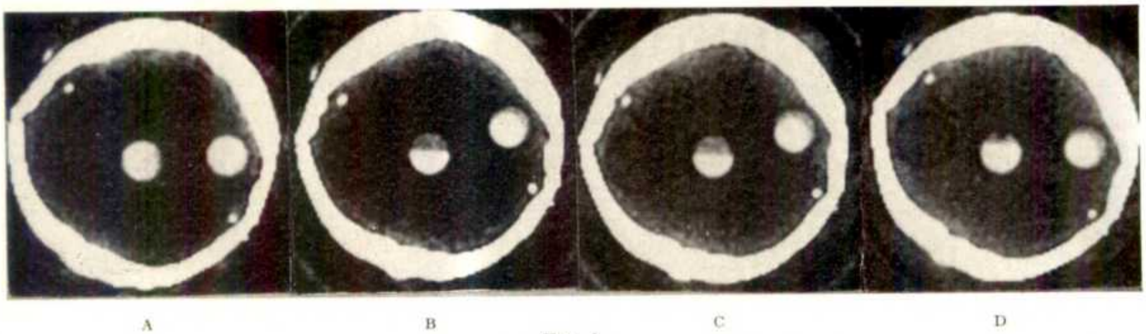


Fig. 1.

Specimens of blood (A) unclotted with heparin (central tube) and (B) clotted. (A) At 15 minutes after being taken the clot has not commenced to contract, the specimens are similar and homogenous. mu a=26.6 mu b=29.5. (B) After three hours there is a level in the heparinized blood due to sedimentation of cells. A crescentic low attenuation region is shown in the plain blood due to serum expressed from the contracted clot which has therefore increased in attenuation. mu a=32.5 mu b=40.7. (C) There is no further contraction or change in attenuation after six hours. mu a=32.3 mu b=41.6. (D) Three days. mu a=35.2 mu b=41.8.

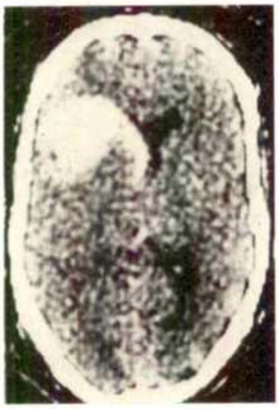


Fig. 2.

Plain CT two days after haemorrhage. Large left frontal haematoma with extension to left frontal horn.

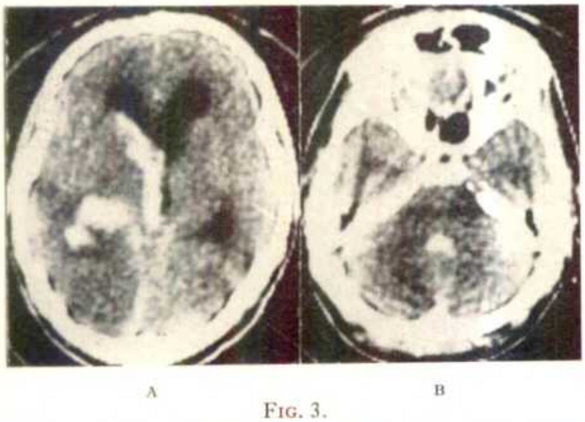


Fig. 3.

Plain scan three days after haemorrhage into left parietal lobe. (A) At level of IVth ventricle and (B) at level of IIIrd. There is extension of haematoma into the left lateral, IIIrd and IVth ventricles.

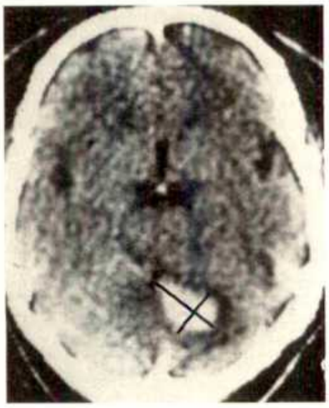


Fig. 4.

Right cerebellar hemisphere haematoma. Plain CT at level of maximum area of haematoma showing sites of measurement of region of increased attenuation as described in text. Similar measurements were made of the outer border of the well defined region of low attenuation.

An approximation to the size of the recent intracerebral haematomas confined to the cerebral substance was obtained by measuring the longest axis of the region of increased attenuation and its greatest width at 90° to this axis. (Fig. 4). A correction factor was applied for the diminution of the images and the figures were multiplied together. The cases were divided into three groups by approximate size.

(A) Less than 10 sq cms
(B) Between 10 and 20 sq cms
(C) Above 20 sq cms

The areas enclosed by the outer border of the well defined region of low attenuation (LAR) around the clot was similarly measured. Assuming approximate symmetry in the vertical plane, an estimate of the relative volume of this region and that of the clot could be made by taking the square root of the area and expressing the volume as the cube of this.

The mu in the central pixels of large clots up to five days old and which were entirely confined to cerebral substance and the EMI number corresponding to the haemoglobin value in the patient's blood taken close to the time of haemorrhage, calculated by using the figures from New and Aranow (1976), were chartered. If one assumes that an intracerebral haemorrhage takes place as a single episode lasting only a few minutes the relative volume of the precontracted clot can be deduced from a ratio between these EMI values (*vide infra*). This ratio was multiplied by the volume of the haematoma calculated as described and the result was compared with the volume enclosed by the outer border of the LAR (Radue and Kendall, 1978).

A few patients were examined in different head positions to study postural variation in the shape of the clot and/or movement within the low attenuation region for any indication of (a) whether the clot itself was solid or semiliquid and (b) the presence of fluid in the LAR, which has been postulated. (Gonzales *et al.*, 1976).

The amount of surrounding "oedema" and its relationship to other features was noted.

The characteristics of any enhancement following intravenous contrast injection was noted.

The patients were divided into three groups by the situation of the haematomas on CT as follows:

Group I involved the internal capsule, thalamus, caudate nucleus and/or brainstem.
Group II involved the lentiform nucleus and/or external capsule.
Group III involved any more superficial region.

These groups were studied in relationship to the other features previously mentioned and to the eventual outcome of treatment.

TABLE I

TOTAL NUMBER OF PATIENTS 50 (MALE 29/FEMALE 21)

Age in years 8–76 mean 50.6	No of patients	Hyper-tensive	Died
8–39	8	50%	1 (1)
40–59	29	59%	3 (2)
60–76	13	38%	8 (4)

Treatment: surgical evacuation, 23 patients; conservative, 27 patients; ( ) hypertension.

RESULTS

The blood clot *in vitro* contracted and achieved its maximum attenuation by three hours. (Fig. 1).

There were 50 patients with spontaneous haematomas (Table I), 21 females and 29 males, in which underlying pathology was excluded as far as possible by angiography. In 23 this was further confirmed by surgery and in four by autopsy.

The age of the patients ranged from 8–76 years (mean 50.6 years) but 84% were above the age of 40. Twenty-six patients (52%) were hypertensive and of the 12 patients who died as the result of their haemorrhage, seven (58%) were hypertensive. Twenty-seven patients were treated conservatively and in 23 the haematoma was evacuated.

There were 14 haematomas in Group I, six in Group II and 31 in Group III (one case had two haematomas) (Table II). Fourteen patients were in Group A, 22 in Group B and 14 in Group C (Table III). The presence or absence of hypertension did not definitely influence the size of the haematomas; hypertension was more frequent in the deep lesions (74% Group I and 66% Group II), though common in the more superficial ones also (42% Group III).

The CT features influencing prognosis were:

1. Site of haematoma: (Table IV) in Group I 43%, Group II 33% and Group III 16% died. In Group I 50%, Group II 33% and in Group III 43% showed marked improvement. If groups I and II are

TABLE II

Position of haematoma	Group	Total	Hyper-tensive
Internal capsule Caudate nucleus Thalamus Brainstem	I	14	74%
External capsule Lentiform nucleus	II	6	66%
More superficial in cerebral hemispheres (30) or cerebellum (1)	III	31	42%

One case had two haematomas.

TABLE III

SIZE OF HAEMATOMA

Size cm²	Group	Total	Hypertensive
Under 10	A	14	43%
10–20	B	22	59%
Over 20	C	14	50%

Two haematomas in Group C were counted together.

TABLE IV

PROGNOSIS WITH SITE OF HAEMATOMA WITH OR WITHOUT SURGERY

Group	Good	Unchanged	Worse	Total
I	7 (2)	1	6 (1)	14 (3)
II	2 (2)	2 (2)	2 (1)	6 (5)
III	13 (7)	13 (7)	5 (1)	31 (15)
Total	22 (11)	16 (9)	13 (3)	51 (23)*

( ) = Operation
*One patient had two haematomas

TABLE V

PROGNOSIS WITH VARIATION IN SIZE OF HAEMATOMA

Group	Good	Unchanged	Worse	Total
A	8 (3)	4 (1)	2	14 (4)
B	13 (7)	6 (4)	3 (2)	22 (13)
C	1 (1)	6 (4)	7 (1)	14 (6)
Total	22 (11)	16 (9)	12 (3)	50 (23)

( ) = Operation

TABLE VI

PROGNOSIS WITH INTRAVENTRICULAR EXTENSION OF BLEEDING

	Confined to part of one lateral ventricle	More than one lateral ventricle involved	Total
Good	3 (43%)	2 (22%)	5
Unchanged	3 (43%)	2 (22%)	5
Worse or died	1 (14%)	5 (56%)	6
Total	7 (44%)	9 (56%)	16 (100%)

added together and deaths compared with Group III, p=0.062.

2. The size of the haematoma: (Table V) in Groups A and B 58% markedly improved and 14% deteriorated or died. In Group C one patient improved and 50% died. (p=0.016). Combining the size and site, haematomas of less than 20 sq. cm in Group III had the best prognosis (60% markedly improved, 11% died) and large haematomas in Group I the worst prognosis, all except two dying, one remaining unchanged and the other improving.

3. Extension of bleeding into the ventricular system occurred in 32% of all cases: 57% of Group I, 50% of Group II and 16% of Group III. Neither the size of the intracerebral haematomas nor the presence of hypertension was related to intraventricular extension. In seven (Table VI) the intraventricular bleeding was confined to part of one lateral ventricle (Fig. 2) and 43% of these cases showed marked clinical improvement, 43% no improvement, and 14% deterioration or died so that prognosis was not affected. In nine cases the intraventricular bleeding was more extensive; only two (22%) of these cases markedly improved, the remainder having gross residual disability or dying, which differs significantly from those without intraventricular extension (p<0.01). However haematoma filled the third and fourth ventricles in both the cases which improved after intraventricular haemorrhage (Fig. 3). Prognosis was not influenced by the extent of spread beyond one lateral ventricle and such cases are therefore included in a single group.

4. The haematoma was evacuated (Table IV) in the patients in Group II apart from one who was moribund; two of the five (40%) improved. Two of the three patients in Group I (66%) and seven of the

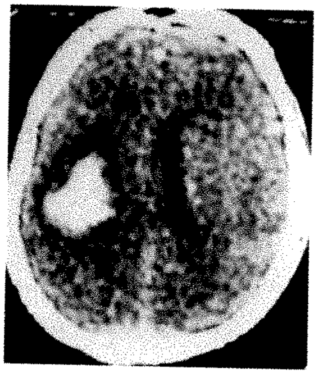


FIG. 5.

Plain CT. Three days after haemorrhage. High attenuation clot in left parietal lobe. Note the clearly defined borders of the peripheral low attenuation zone of ischaemic necrosis. The body of the left lateral ventricle is not shown, being depressed below the plane of the cut by mass effect from the haematoma.

TABLE VII

LOW ATTENUATION

Time from bleeding days	Minimal	Local well defined	More extensive	Total
1– 2	11	13	2	26
3– 4	2	5		7
5– 8	2	7	2	11
9–14			3	3
>14	0	2	1	3
	15	27	8	50

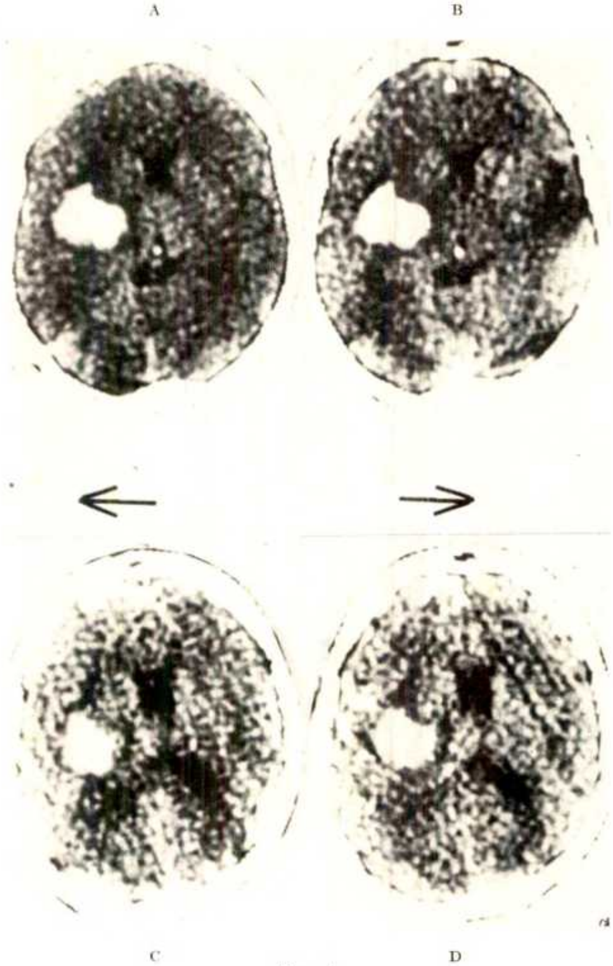


FIG. 6.

Plain scans taken as nearly as possible at the same level (A) with the head turned on the left side, (B) with the head turned on the right side, in a patient with a haematoma five days old. Note that any changes in the haematoma surrounding low attenuation zone are minimal. (C) and (D) similar scans taken nine days later. Note that the attenuation in the periphery of the clot has decreased resulting in some widening of the surrounding zone of low attenuation. There is now slight change in the shape of the haematoma with posture suggesting that there has been some softening. This was one of the more marked postural changes seen in the haematomas suggesting that much of the clot generally remained compact.

15 in Group III (47%) submitted to surgery were improved; the corresponding results in the unevacuated haematomas were 5/11 Group I (45%) and 6/15 Group III (40%). However the effects of surgery are difficult to assess because selection of generally fit patients who were considered to have a relatively good prognosis obviously biased the results.

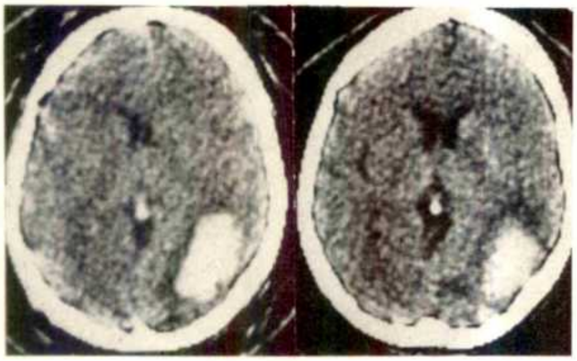
A small well defined zone of low attenuation (8–12 EMI units) was present around most haematomas (Fig. 5) (Table VII); it tended to be narrower in cases scanned on the same day as the bleed. It was not obviously influenced by the site of the haematomas and not directly proportional to the size of the lesions, but tended to be larger with big haematomas. The zone was usually wider anterior to the clot and change with the position of the head was either absent or minimal. (Fig. 6).

The mu in the 1–5 day old large haematomas varied between 28 and 41 EMI units. The haemoglobin readings in the blood of our cases were

TABLE VIII

RATIO BETWEEN ATTENUATION OF PATIENTS' BLOOD (C), CALCULATED FROM THE HAEMOGLOBIN CONCENTRATION, AND MEAN ATTENUATION (MU) IN CENTRE OF LARGE HAEMATOMAS UNDER FIVE DAYS OLD CONFINED TO BRAIN SUBSTANCE

Hb	(c)	mu	$\frac{\text{mu}}{\text{c}}$
10.9	16.1	35	2.1
12.1	16.9	41	2.4
12.1	16.9	30	1.7
12.5	17.5	38	2.1
12.7	17.7	28	1.5
12.8	17.9	32	1.7
13.7	19.1	35	1.8
14.0	19.6	28	1.4
14.2	19.8	39	1.9
14.3	20.0	32	1.6
14.5	20.3	36	1.7
14.7	20.5	33	1.6
15.2	21.2	30	1.4
16.5	23.1	27	1.1
18.3	25.6	34	1.3



A B

FIG. 7.

Plain CT scans taken at same level. (A) Two days after haemorrhage. There is a right posterior temporal haematoma, extending into the occipital region, with adjacent well defined region of low attenuation. (B) Twenty-six days after haemorrhage. There has been diminution in attenuation throughout the clot, more marked peripherally, so that the high attenuation zone is smaller. There is widening of the low attenuation zone, though the extent of the whole lesion is unchanged.

between 10.9 and 18.3 grams corresponding to calculated EMI attenuation range of 16.1–25.6. The mu in the clots was not proportional to the original haemoglobin concentration in the blood (Table VIII). The volume enclosed by the LAR around these haematomas varied between 40 and 106% (mean 72.4%) of the precontraction volume of the haemorrhages calculated as described.

Two or more scans were available on 14 individual patients treated conservatively. The first scan was taken 1–10 days after onset and the subsequent ones after an interval of 3–21 days, in 13 of these the other being after six months. The combined size of the region of increased and surrounding low attenuation was never larger on the second scan than on the first but the LAR increased in width due to diminuation of the area of high attenuation, confirming that the widening was due to changes in the clot, most evident at the periphery (Fig. 7).

Reduction in attenuation to isodensity with brain sometimes progressing to a residual low attenuation region is an extension of this process. As one would expect, the sequence is more rapid with small haematomas.

More distant and poorly demarcated low attenuation (Table VII) occurred in only eight cases. This was not related to the site of the intracerebral haematoma (Courville and Friedman, 1942) or to the presence or absence of hypertension. It was more frequent with large haematomas, but it did occur with small ones. The two cases in which it occurred on the first and second day, both died; in the others it did not obviously affect prognosis, three improved and three remained unchanged. In one of these cases a left frontal haematoma had extended into the subarachnoid space; arteriography showed spasm of both anterior cerebral arteries and there was low attenuation without mass effect in both frontal lobes (Fig. 8) which had a time course suggesting infarction. Indeed it is not possible to be sure that some of these patients had not suffered haemorrhagic infarcts. Points against this are no occluded artery on any of the angiograms, and the solitary and compact homogenous appearance of the clot on CT.

Autopsy on the two who died and observation at surgery in one other did not show evidence of infarction. The ventricular displacement caused by haematomas (Table IX) was generally proportional to their size; ventricular compression was also influenced by site, but not markedly by the degree of surrounding low attenuation, which may be considered to be in favour of widespread low attenuation being due to infarction rather than oedema.

Contrast medium was given in 22 cases between 1 and 28 days after the haemorrhage. Peripheral ring enhancement within or involving the region of low attenuation occurred in seven cases; it was slight in three of them at six, six and 14 days from onset and more conspicuous but still modest around resolving haematoma at 17 and 28 days after onset. The sixth patient was scanned eight weeks after an intracerebral and subarachnoid haemorrhage. The scan showed an isodense mass in the left lentiform region

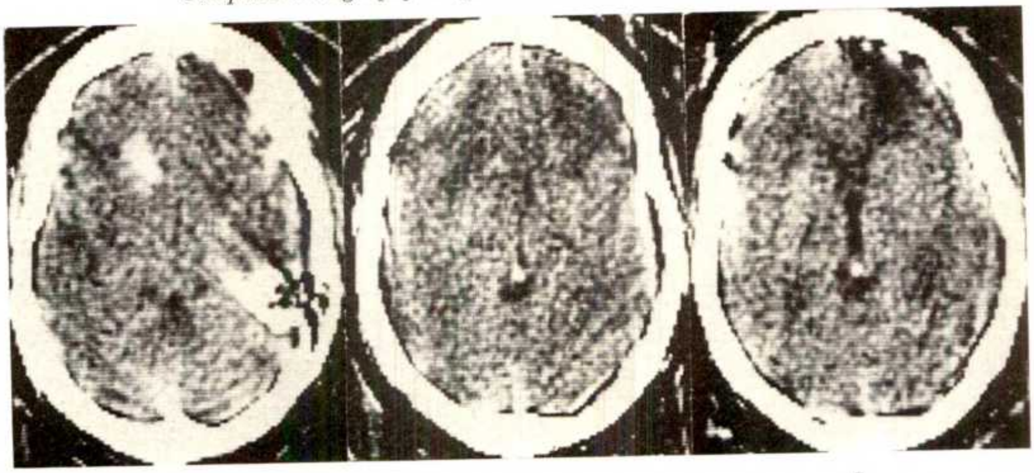


FIG. 8.

(A) Plain scan ten days after haemorrhage. There is a left inferior frontal haematoma. (B) Cut immediately above showing low attenuation in both frontal lobes. Angiography on the same day as the scan showed spasm of both anterior cerebral arteries. (C) Plain scans at similar level to (A) and (B) taken 13 days later. The high attenuation in the left frontal lobe has almost resolved. The low attenuation persists and is better defined. Repeat angiography on same day showed continuing spasm of the anterior cerebral arteries. The appearances and time course suggest infarction.

TABLE IX

RELATION BETWEEN MASS EFFECT AND SIZE OF HAEMATOMA

Time from ictus	Total	No mass effect	Ventricle compressed	Midline displaced
1–2 days	26	5 (4A, 1B)	9 (5A, 3B, 1C)	12 (3B, 9C)
1–2 days	7	1 (1A)	3 (3B)	3 (2B, 1C)
5–8 days	11	3 (2A, 1B)	3 (2A, 1B)	5 (3B, 2C)
9–14 days	3	1 (1A)	1 (1A)	1 (1C)
over 14 days	3		1 (1A)	2 (1A, 1B)
	50	10	17	23

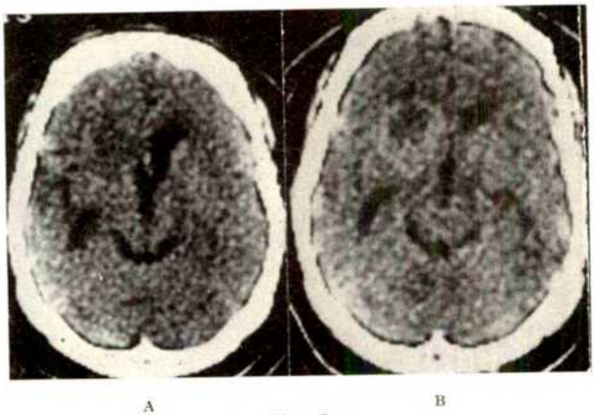


FIG. 9.

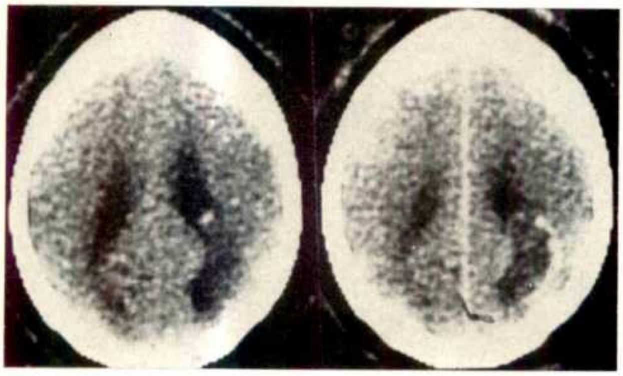
A) Plain scan eight weeks after intracerebral and subarachnoid haemorrhage. There is a focal low attenuation lesion in the left caudate region, compressing the left frontal horn. (B) After intravenous contrast medium. There is ring enhancement around the resolving haematoma.

with a ring blush after enhancement (Fig. 9). In the last case the enhancement was in the margin of a low attenuation region at the site of a haematoma, 14 weeks after bleeding (Fig. 10).

DISCUSSION

The clinical features of our patients are similar to those in large recorded series. The age range overlaps that of aneurysmal and angiomatous haemorrhage; the average and peak age of spontaneous haemorrhage is 20–30 years older than that from angiomas (Perret and Nisihioka, 1966, Kendall and Claveria, 1976), but was similar to that occurring from aneurysms (Sahs *et al.*, 1969).

The sites of the spontaneous haematomas is compared with those from previously collected consecutive scans on patients with haematomas from AVMs and aneurysms in Table X. The commonest



A B

Fig. 10.

(Same case as Fig. 7). (A) Plain scan. (B) After intravenous contrast medium. Enhancement round margin of a low attenuation region at the site of previous haematoma, 14 weeks after bleeding.

TABLE X

Location of centre of haematoma

	Spontaneous	AVM	Aneurysm
Group I	14 (28%)	4 (11%)	1 (2%)
Group II	6 (12%)	2 (6%)	3 (6%)
Temporal	8 (16%)	5 (14%)	18 (36%)
Frontal	3 (6%)	5 (14%)	21 (42%)
Parietal	14 (28%)	10 (28%)	1 (2%)
Occipital	5 (6%)	5 (14%)	
Cerebellum	1 (2%)	2 (6%)	
Brainstem		1* (2%)	2* (6%)
Callosal/Septal		2 (6%)	6 (12%)
Total	51	35	50

*Also included in Group I

position of haematomas of all aetiologies was in Group III. This distribution is somewhat artificial because in a secondary referral centre like the National Hospital there is a bias towards selection of the potentially more treatable cases and also many capsular and basal ganglion haematomas, especially those in hypertensive patients, which are likely to be spontaneous are not subjected to angiography after CT; during the period of the study this applied to over a third of Group I and II haematomas. An aneurysmal origin may be suspected when haematomas extend near the region of the circle of Willis especially in the inferior frontal and anterior temporal regions. The distribution is discussed in detail by Hayward and O'Reilly (1976). Haemorrhages in Group I and II distribution are most frequently spontaneous, though 8% of haematomas of aneurysmal origin, usually from middle cerebral aneurysms bleeding into the lentiform—external capsular region, and 14% from angiomatous malformations, occurred in this distribution in our series.

The haematomas themselves were generally similar regardless of aetiology. Clotting of normal blood takes place within minutes of extravasation and maximum retraction of the clot is usual within three hours. The volume of clot, as expected from *in vitro* observations, is confirmed by attenuation readings taken entirely within some large haematomas, which varied between 28 and 41 EMI units, to be 40–70% of that of the extravasated blood. The CTs on all our cases were made more than six hours after the stroke, so that the haematoma was assumed to have maximally contracted and this was confirmed in those cases with follow-up studies, none of which showed any increase in attenuation in the clotted blood. A further case was seen during the time of this survey in which intracerebral bleeding associated with a high dose of heparin had occurred four hours previous to CT. The attenuation (mu 26) was close to that of unconcentrated blood apart from a layer posteriorly where it was increased (mu 28) due to some sedimentation of cells (Fig. 11).

It is very difficult to obtain exactly comparable scans taken with variation of head position but our cases show that there was no change in most clots examined in the first few days but slight change in the shape of others suggesting that some liquefaction did occur, but they remained mostly compact. There was probably minimal, but never definite movement of the high attenuation mass within the LAR suggesting that this zone does not contain a significant amount of free fluid. After several days the width of the LAR increases due to changes in the periphery of the clot including breakdown of the haemoglobin

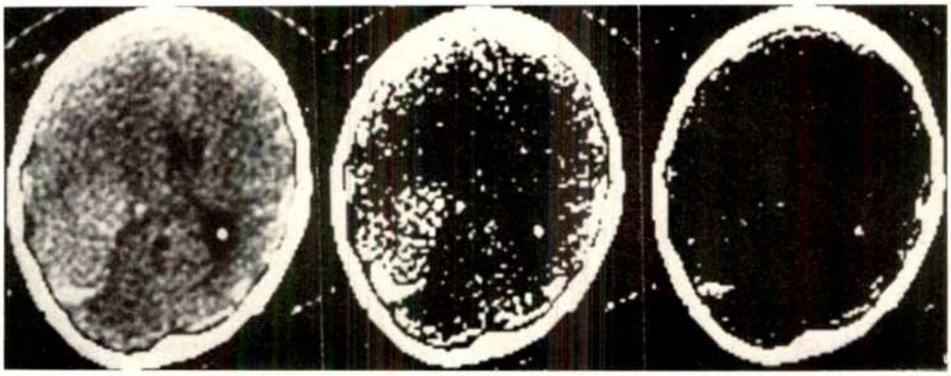


FIG. 11.

Plain scan, same cut. (A) L18 W40 (B) L20 W1 (C) L28 W1. Four hours after intracerebral haemorrhage, patient on heparin therapy to cover mitral valve replacement. Haemoglobin 14g. Large haematoma with attenuation mu 26 slightly higher reading in a posterior layer (mu 28) is presumably due to precipitated cells. The low attenuation zone is very narrow, in keeping with minimal clot retraction.

or fibrinolysis. The low attenuation immediately adjacent to a haematoma in early scans, corresponding to the zone of ischemic necrosis commonly seen at autopsy, is consistent with the effects of acute pressure from the haemorrhage in the time prior to clot retraction.

We acknowledge that calculation of the precontracted volume of the haematoma as described is a crude approximation and is subject to several errors. For example:

1. Extravasation of angiographic contrast medium has been shown in 11–12% of spontaneous hypertensive haematomas (Huckman *et al.*, 1970, Yamaguchi *et al.*, 1971). It is seen most frequently when angiograms are performed within the first five hours after onset of a stroke. Though it may be argued that such extravasation was precipitated by angiography, it is probable that intracerebral haemorrhage may sometimes continue for several hours. In such cases contraction of the original clot and absorption of fluid from it could be occurring while continuing haemorrhage would be tending to increase its volume. In such a case calculation of precontraction volume based on attenuation readings would be too large. The calculated precontraction volume was larger than the LAR in most of our recent haematomas. This may be suggestive evidence that these cerebral haemorrhages take place over several hours rather than being instantaneous, or it may indicate that only a part of that brain tissue compressed by the haemorrhage is damaged sufficiently to show CT changes.

2. The haemoglobin level at the site of bleeding could have differed from that recorded close to but not precisely at the time of haemorrhage. There is evidence to suggest that the haematocrit value in the cerebral arteries is 8–16% lower than in systemic veins (Grubb *et al.*, 1973); we made a standard allowance of 12% for this.

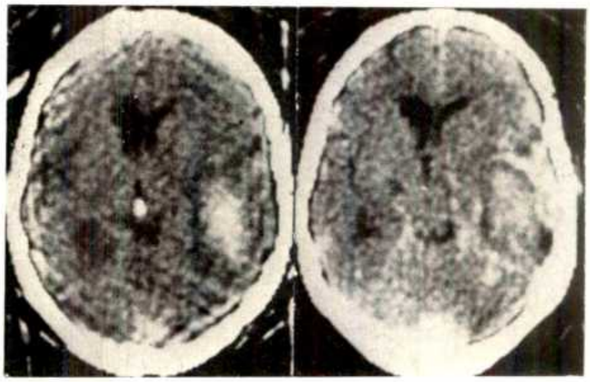


FIG. 12.

CT six days after haemorrhage. (A) Plain scan: there is a haematoma in the right posterior temporal region causing compression of the right lateral ventricle and slight mid-line shift. (B) Slightly lower level after intravenous contrast medium. There is enhancement around the haematoma with curvilinear densities extending towards the convexity. These appearances strongly suggest an angiomatous malformation adjacent to the haematoma. Angiography failed to confirm the malformation but it was revealed at surgery.

3. Partial volume effects could have interfered with attenuation readings. Every effort was made to avoid this by using only large haematomas and measuring only the central parts of these.

4. It was not practical to make accurate measurements of the complex areas of the haematomas and surrounding LAR and even small errors would

be significant because of conversion to volumes. The importance of this was decreased to some extent by dealing with ratios rather than absolute measurements. Because of the combination of these factors, we did not expect to find any precise relationship between the calculated size of the original clot and that of the well defined low attenuation zone. It was therefore not unexpected that the LAR was between 40% and 100% of the volume of the original clot.

The LAR around haematomas is typically local and relatively small, but in our experience, more extensive ill defined low attenuation occurred in 16% of spontaneous haematomas and in 27% of haematomas associated with aneurysms. Subarachnoid haemorrhage, associated with angiographic evidence of arterial spasm was present in some of these cases and it may be that spasm influences the amount of low attenuation by causing ischaemia. The difficulty of excluding some of our cases being haemorrhagic infarcts and the reasons for considering them to be primary haemorrhages has been mentioned previously. Increase in mass effect, thought to be due to oedema, has been seen on sequential angiograms obtained within three weeks of onset of hypertensive intracerebral haemorrhages (Yamaguchi *et al.*, 1973). This phenomenon was not observed on CT in our cases; most of our spontaneous haematomas were on steroid therapy and this may have modified the formation of oedema.

The factors affecting prognosis were, in general, similar to those noted by other authors. CT has shown that localized intraventricular extension of bleeding does not worsen the prognosis. More generalized intraventricular spread is a bad prognostic sign, but 22% of our cases made good recoveries. Extension of blood into the third and fourth ventricles is not necessarily fatal as has been previously

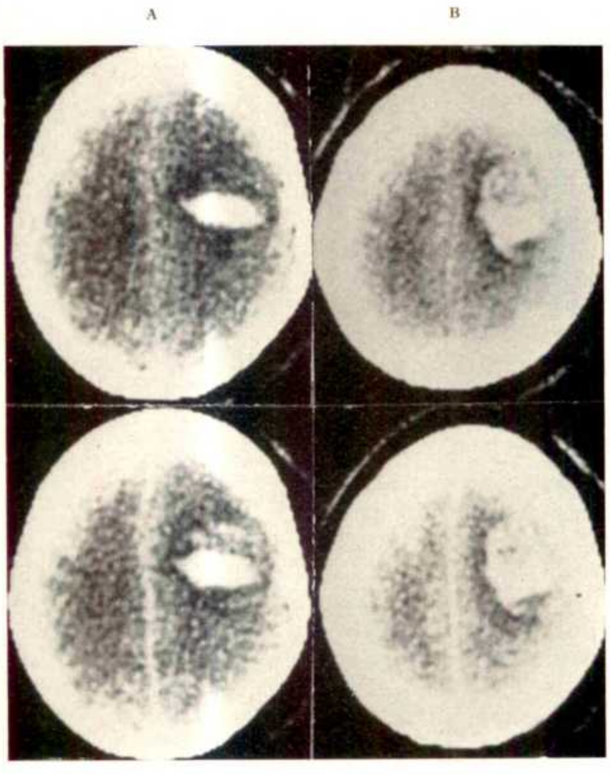


FIG. 13.

(A) and (B) Plain scan adjacent levels two days after intracerebral haemorrhage. There is a right posterior fronto-parietal haematoma with adjacent low attenuation. (C) and (D) Same levels after intravenous contrast medium. There is a wide region of enhancement beyond the haemorrhage and this has occurred too early for reaction to a spontaneous haemorrhage, suggesting underlying pathology. Haemorrhage into a glioma was found at surgery.

suggested (Pia 1971). Group I haematomas and those above 20 sq. cm had a worse prognosis than the other groups.

Gradual reduction of attenuation within clot to isodense and eventually low attenuation, discussed by Messina and Chernick (1976) has been followed in several of our cases. Contrast enhancement around resolving haematomas (Messina 1976; Zimmerman *et al.*, 1977) due to loss of autoregulation, damage to the blood brain barrier and/or granulation tissue extending from the periphery into the clot is also well known. It causes no diagnostic difficulty when there is a central mass of increased attenuation on the same or previous scans or when there is an appropriate history suggesting subarachnoid haemorrhage. Occasionally these more specific features are absent and then the combination of a lesion of near brain density with ring enhancement on the first CT study may be indistinguishable from other pathologies; haemorrhage should always be considered as one cause of this appearance in appropriate cases.

During the period of this study two further patients with intracerebral haematomas were considered possibly to be spontaneous prior to surgery. One of these was diagnosed on CT as having a haematoma associated with an angiomatous malformation (Fig. 12) because of marked and diffuse enhancement extending into the haematoma. However no malformation could be shown at complete and detailed angiography but one was found in the haematoma cavity at surgery.

The second was a woman aged 40 who had been normal prior to the acute haemorrhage which occurred two days prior to CT. This revealed a haematoma with considerable surrounding low attenuation. (Fig. 13). There was irregular enhancement in the low attenuation region, which was both unusually extensive and occurred too early after the bleeding for reaction to a spontaneous haematoma. Haemorrhage into a glioma was considered likely, but angiography failed to confirm showing only an avascular mass. A glioma with a haemorrhage within it was found at surgery.

An angiomatous malformation associated with the haematoma may be suspected if enhancement is more diffuse within and around a haematoma or is associated with adjacent tubular densities due to enlarged vessels (Kendall and Claveria, 1976); such appearances may be important pre-operative evidence of an AVM when thrombosis or clot compression prevents filling on technically good angiography (Kramer and Wing, 1977). It should be noted that enhancement due to haematoma alone has not occurred earlier than the sixth day after haemorrhage and that it is confined to the region immediately adjacent to the haematoma: earlier or more extensive enhancement should suggest the probability of an underlying intracerebral tumour or angioma.

REFERENCES

COURVILLE, C. B., and FRIEDMAN, A. P., 1942. Haemorrhages into the lateral basal ganglion region: their relationship to recovery from cerebral apoplexy. *Bulletin of Los Angeles Neurological Society*, *7*, 137–149.

GONZALES, C. F., GROSSMAN, C. B., and PALACIOS, E., 1976. *Computed brain and orbital tomography*. John Wiley and Sons, Inc. New York.

GRUBB, R. L., PHELPS, M. E., and TER POGOSSIAN, M., 1973. Regional cerebral blood volume in humans: X-ray fluorescence studies. *Archives of Neurology*, *28*, 38–44.

HAYWARD, R. D., and O'REILLY, G. V. A., 1976. Intracerebral haemorrhage. *Lancet*, *1*, 1–4.

HUCKMAN, M. S., WEINBERG, P. E., KIM, K. S., and DAVIS, D. O., 1970. Angiographic and clinico-pathologic correlates in basal ganglionic haemorrhage. *Radiology*, *95*, 79–92.

KENDALL, B. E., and CLAVERIA, L. E., 1976. The use of computed axial tomography for the diagnosis and management of intracranial angiomas. *Neuroradiology*, *12*, 141–160.

KRAMER, R. A., and WING, S. D., 1977. Computed tomography of angiographically occult cerebral vascular malformations. *Radiology*, *123*, 649–652.

MESSINA, A. V., 1976. Computed tomography: contrast enhancement in resolving intracerebral haemorrhage. *American Journal of Roentgenology*, *127*, 1050–1052.

MESSINA, A. V., and CHERNICK, 1976. Computed tomography: the "resolving" intracerebral haemorrhage. *Radiology*, *118*, 609–613.

NEW, F. P., and ARANOW, S., 1976. Attenuation measurements of whole blood and blood tractions in computed tomography. *Radiology*, *121*, 635–640.

NORMAN, D., PRICE, D., BAYD, D., FISHMAN, R., and NEWTON, T. H., 1977. Quantitative aspects of computed tomography of the blood and cerebrospinal fluid. *Radiology*, *123*, 335–338.

PERRET, G., and NISIHIOKA, H., 1966. Report on the cooperative study of intracranial aneurysms and subarachnoid haemorrhage Section 6. Arteriovenous malformation; an analysis of 545 cases of craniocerebral arteriovenous malformations and fistulae reported to the co-operative study. *Journal of Neurosurgery*, *25*, 467–490.

PIA, H. W., 1971. *The operative treatment of intracerebral haematoma*. Proceedings of the Fifth European Congress of Neurological Surgery, Prague.

RADUE, E. W., and KENDALL, B., 1977. *Some observations in spontaneous intracerebral haematomas in C.T.* Proceedings of 6th Internationales Symposion zur Koordination der neurologischen Wissenschaften. H. Gänshirt, Heidelberg.

SAHS, A. L., PERRET, G. E., LOCKSLEY, H. B., and NISHIOKATT, 1969. *Intracranial aneurysms and subarachnoid haemorrhage*. J. B. Lippincott Company, Philadelphia and Toronto.

YAMAGUCHI, K., UEMURA, K., TAKAHASHI, H., KAWADA, M., and KUTSUZAWA, T., 1971. Intracerebral leekage of contrast medium in apoplexy. *British Journal of Radiology*, *44*, 689–691.

YAMAGUCHI, K., UEMURA, K., and TAKAHASHI, H., 1973. An angiographic study of sequential changes in hypertensive intracerebral haemorrhage. *British Journal of Radiology*, *46*, 125–130.

ZIMMERMAN, R. D., LEED, N. E., and NAIDICH, T. P., 1977. Ring blush associated with intracerebral haematoma. *Radiology*, *122*, 707–711.

1978, *British Journal of Radiology*, *51*, 574–578

The hip joint in Paget's disease (Paget's "coxopathy")

By P. B. Guyer, D.M., F.R.C.P., F.R.C.R., and K. C. Dewbury, F.R.C.R.

X-ray Department, Royal South Hants Hospital, Southampton

(*Received January, 1978*)

ABSTRACT

Three hundred patients with Paget's disease around the hip joint are compared with 300 control patients who did not have Paget's disease. The incidence of joint degeneration in the two groups is similar at all ages, and there appears to be no predisposition to joint degeneration in patients who have Paget's disease. A feature of the hip joints is that in approximately half there is joint narrowing to less than 3 mm affecting a portion or the whole of the joint surface, which, together with the incidence of protrusio acetabuli, is probably a specific manifestation of the joint changes associated with Paget's disease.

Although changes in the hip joints in patients who have Paget's disease in the pelvis or femur have been frequently reported in the continental literature (Dubois and Francois, 1960; Walko, 1961; Recordier *et al.*, 1963; Serre *et al.*, 1963), very little on this subject has appeared in the English literature. Machtey *et al.*, (1966) reviewed 57 patients and concluded that the radiological changes resulted from weakening and deformity of the bones. Roper (1971) recorded 23 patients seen at the Royal National Orthopaedic Hospital over a period of eight years, and stated that clarification of the relationship between Paget's disease and degeneration of the hip joint would help in the management of these patients. He considered that involvement of the acetabulum was of prime importance. Barry (1973) stated: "There is no good evidence that the development of osteoarthritic changes in the hip or knee are more likely to occur in patients suffering from Paget's disease than in other elderly members of the community".

During a large survey of the prevalence of Paget's disease (Barker *et al.*, 1977; Guyer and Clough, 1978), the opportunity arose to examine the hip joint changes in these patients, the bones for trabecular enhancement (O'Reilley and Race, 1932) and the soft tissues for arterial calcification (de Deuxchaines, and Krane, 1964). Both it has been suggested, are more common in patients with Paget's disease.

METHODS

Four hundred patients with Paget's disease were collected from amongst patients attending the X-ray Departments in Southampton. Of these, 300 had Paget's disease either in the pelvis or in the femur. This was detected as a result of skeletal X-ray examinations in 142 patients, and plain films or contrast examinations of the abdomen in the remaining 158. A series of 300 unselected patients without Paget's disease was also collected from our X-ray files; these were matched for age and sex with the Paget's patients. In this latter group there were 136 examinations performed for examination of the skeleton, and 164 plain films of the abdomen or contrast examinations. Both series were examined in detail for evidence of degenerative disease in the hip joints. In addition, the hip joints in the Paget's group which were unaffected by the bone disease were used to provide a second control group. The width of the joint was measured in each patient, the narrowest measurement being taken or, in the absence of any narrowing, the width of the joint at the junction of the superior and medial compartments of the joint. All joints which were not absolutely normal radiologically were classified into three groups. Firstly, there were those with joint narrowing only. Secondly, there were those with "minimal" degeneration consisting only of a little cystic change, osteophytic lipping, or joint surface irregularity in the lateral aspect of the acetabulum (Fig. 1). In the third group the changes were more severe or more extensive than this and they were grouped together as

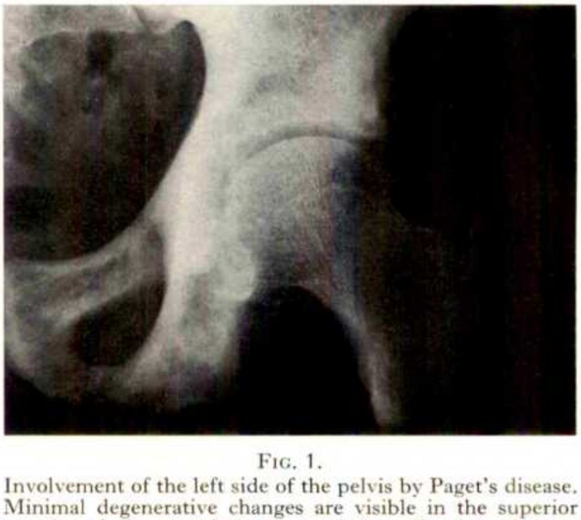


FIG. 1.

Involvement of the left side of the pelvis by Paget's disease. Minimal degenerative changes are visible in the superior margin of the acetabulum, consisting of minimal joint irregularity and cyst formation, but there is no joint narrowing. There is thickening of the ileo-pectineal line (the "brim" sign).

"more advanced". In all patients with Paget's disease any thickening of the ileo-pectineal line (the "brim" sign of Gutman and Kasabach, 1936; Dickson *et al.*, 1945; Marshall and Ling, 1963; and Graham and Harris, 1971) or protrusio acetabuli was also recorded. The femoral necks were examined for evidence of enhancement of the trabecular pattern. The soft tissues were examined for evidence of arterial calcification in the aorta and its abdominal and pelvic branches. The frequency and severity of hip joint changes were assessed in patients with pelvic or femoral Paget's disease alone, and when the two occurred together. The request cards were examined for evidence of symptoms referable to the hip joints.

RESULTS

There were 300 patients with Paget's disease and 300 controls without the disease. In each group there were seven males and two females aged under 55, 20 males and 16 females aged between 55 and 64 years of age, 58 males and 41 females aged between 65 and 74, 59 males and 60 females aged between 75 and 84 years, and 18 males and 19 females aged 85 years or more. Because some of the patients with Paget's disease had only one joint affected by the bone disease, the total number of hip joints with adjacent Paget's disease was 420. There were 180 hips in this group without adjacent Paget's disease, providing one control group; the age-matched series of 300 patients provided a further 600 joints for comparison. The results of the analysis of these hip joints is shown in Table I, where it can be seen that the prevalence of joint normality, minimal degeneration, and more advanced degeneration is of the same order in patients with Paget's disease and in the two control groups. In all groups there was a similar proportion of minimal and more advanced degeneration in successive age groups. The joint narrowing showed no age-related trend.

Joint narrowing at some point to a measurement of less than 3 mm (Machtey *et al.*, 1966) occurred in 188/422 hips (44.5%) of patients with Paget's disease, but in only 45/600 hips (7.5%) and 9/180 of

TABLE I

THE SERIES

	Normal (%)	Joint Narrowing Alone (%)	Minimal Degeneration (%)	More Advanced Degeneration (%)	Total Hips
Paget's Patients					
a) Hip joints with adjacent Paget's disease					
Age (years) less than 55	3(27.3)	3	5(45.4)	—	11
55–64	7(16.3)	11	22(51.2)	3(6.9)	43
65–74	16(11.2)	11	112(78.8)	3(2.1)	142
75–84	8 (4.8)	3	140(84.8)	14(8.4)	165
over 84	1 (1.7)	—	51(86.4)	7	59
	35	28(6.6)	330(78.6)*	27(6.4)	420
b) Hip joints without adjacent Paget's disease					
Age (years) less than 55	2(28.6)	1	4(57.1)	—	7
55–64	8(27.6)	—	20(68.9)	1(3.4)	29
65–74	12(21.4)	—	43(76.8)	1(1.7)	56
75–84	4 (5.4)	—	67(91.1)	2(2.7)	73
over 84	2(13.3)	—	12(80.0)	1(6.6)	15
	28(15.5)	1(0.5)	146(81.1)†	5(2.7)	180
Control patients					
Age (years) less than 55	6(33.3)	—	12(66.6)	—	18
55–64	11(15.3)	1	60(83.3)	—	72
65–74	27(13.6)	1	158(79.7)	12(6.0)	198
75–84	19 (7.9)	1	193(81.1)	25(10.5)	238
over 84	6 (8.1)	2	57(77.0)	9(12.1)	74
	69(11.5)	5(0.8)	480(80.0)‡	46(7.6)	600

*160 also had joint narrowing.
†20 also had joint narrowing.
‡45 also had joint narrowing.

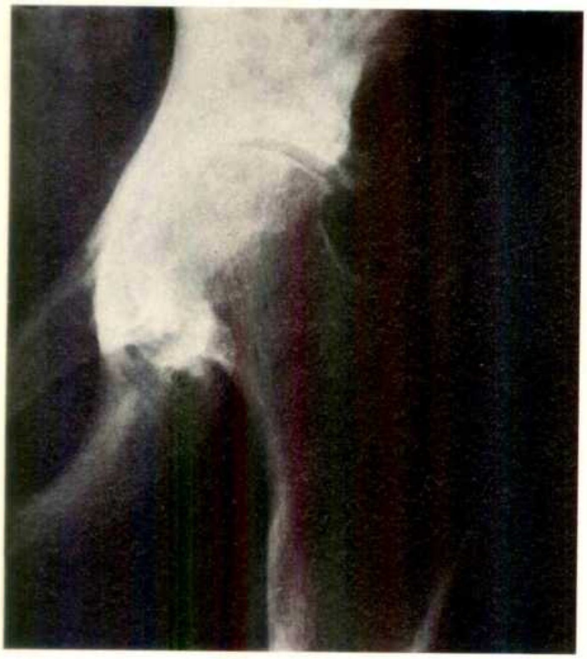


Fig. 2.

Involvement of the left side of the pelvis by Paget's disease with widespread joint narrowing, particularly affecting the medial compartment of the joint. There is minimal degeneration affecting the outer lip of the acetabulum. The ileo-pectinal line is thickened.

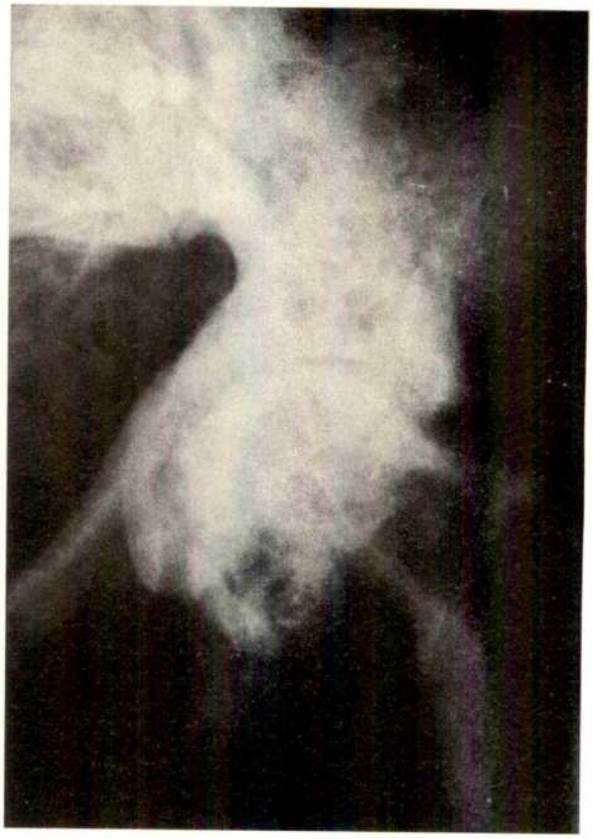


Fig. 3.

The left side of the pelvis and the femur are involved. There is concentric joint narrowing, thickening of the ileo-pectinal line, and early protrusio acetabuli.

the control groups. It was an isolated feature in 28/422 (6.6%) of hips in patients with Paget's disease (Table I), and in 5/600 (0.8%) and 2/180 (1.0%) of the control patients. Joint narrowing occurred with evidence of joint denegeration in a further 160 hips of patients with Paget's disease, and in 40/600 and 7/180 hips of the control groups. In 76 of all the hips with adjacent Paget's disease the narrowing was localized to a short area of the joint surface; in 77 it was widespread, involving especially the medial compartment of the joint (Graham and Harris, 1971) and in 35 it was concentric (Figs. 2 and 3).

Table II analyses the hip joint changes according to whether or not the pelvis or femur alone were affected by Paget's disease, or whether the bones on both sides of the joint were affected. From this it can be seen that there is a similar extent of minimal degeneration in all three situations, but that narrowing of the hip joint only occurred if the acetabulum was involved.

Diffuse thickening of the ileo-pectineal line—the "brim" sign—was present in 376 of 384 hips with involvement of the pelvis (Figs. 1–3). The sign indicates thickening of the bone due to the Paget's process, and is not to be confused with protrusio acetabuli. We did not see this sign in either control group.

Protrusio acetabuli was diagnosed when there was localized projection of the acetabulum into the pelvic cavity (Fig. 3). It occurred in 60 hip joints of patients with adjacent Paget's disease, 12 patients having both joints affected, 36 patients with only one joint affected. In two joints there were no other changes of either degeneration or narrowing, and the joints were therefore otherwise radiologically normal. In 44 of the joints the degenerative changes were classified as minimal, and in seven as more advanced. In seven joints, joint narrowing was the only other detected abnormality.

Symptoms of hip joint degeneration were recorded on the request cards of 27/300 (9%) of patients with Paget's disease adjacent to the hip joint, and in 37/300 (12.3%) of the control patients.

Prominent trabeculation in the femoral necks was noted in 18 male patients with Paget's disease

TABLE II

JOINT DEGENERATION RELATED TO EXTENT OF PAGET'S DISEASE

	Normal (%)	Narrowing Alone	Minimal Degeneration (%)	More Advanced Degeneration (%)
Pelvic Paget's Alone (276 hips)				
Age (years) under 55	2	3	3	—
55–64	6	9	13	3
65–74	12	7	66	2
75–84	6	3	87	7
over 84	1	—	30	6
Total hips	27(9.8)	22	209(75.7)	18(6.5)
Femoral Pagets' Alone (36 hips)				
Age (years) under 55	1	—	1	—
55–64	—	—	4	—
65–74	2	—	11	—
75–84	—	—	12	2
over 84	—	—	3	—
Total hips	3(8.3)	—	31(86.1)	2(5.5)
Pelvis & Femur Affected (108 hips)				
Age (years) under 55	—	—	1	—
55–64	1	2	5	—
65–74	2	4	35	1
75–84	2	—	31	5
over 84	—	—	18	1
Total hips	5(4.6)	6	90(83.3)	7(6.5)

compared with ten of the control series, and in 29 female patients compared with 18 controls.

Arterial calcification was noted in 81 males with Paget's disease compared with 76 of the male controls, and in 78 and 62 of the female patients respectively.

DISCUSSION

Our initial impression on examining the hip joints in patients with Paget's disease was that radiological abnormalities were much more common in patients with the disease than in the control series. This was in fact found to be so, but when the changes of minimal and more advanced osteoarthrosis of the hip joints were compared it was found that there was a similar incidence of degenerative disease in the Paget's patients and in the controls. The high frequency of abnormal joints reflects the inclusion of any joint which was not entirely normal; many of these changes were very minor and would not normally have been commented upon, but we found that reliable subdivision of these changes was impracticable.

The difference between our initial impression and the fact that fewer showed minimal changes only was due to a high incidence of joint narrowing to less than 3 mm joint space in patients with Paget's disease, and indeed this was the only radiological abnormality in 28 patients with Paget's disease. Altogether joint narrowing of less than 3 mm occurred in 188 of 422 hips in patients with Paget's disease adjacent to the hip joint, compared with 45/600 and 9/180 of the control hips. This joint narrowing was measured at the point of maximal visible narrowing whether this was in the superior, medial or inferior compartment of the joint. Not all authors would agree with the inclusion of narrowing of the superior compartment of the joint (Roper, 1971), maintaining that this is a common feature of primary degeneration (osteoarthrosis) of the hip joint. However, we feel that our decision to include joint narrowing due to Paget's disease is supported by the differences we found in the joint narrowing between the groups. Even though minimal degeneration was present in similar proportions of those with adjacent Paget's disease and those without it, joint narrowing was much more common in those with the primary bone disease, and it therefore seems that joint narrowing is a specific feature of involvement of the hip in patients with Paget's disease of the pelvis. This feature occurred exclusively in patients with involvement of the acetabulum by the bone disease, there being no patient with involvement of the femur alone who showed any joint narrowing, a finding in keeping with the comments made by Machtey *et al.* (1966) and Roper (1971).

When the figures for patients with Paget's disease are compared with controls, the incidence of degenerative disease of the hip joint is similar at all ages. Since there are no major differences we conclude that there is no predisposition to joint changes in patients with Paget's disease, other than joint narrowing. Steinbach (1961) suggested that this might be due to increased subchondral ossification, offering no explanation why this should occur, and both he and Machtey *et al.*, (1966) suggested that joint narrowing was due in part to pressure on the joint surfaces.

Protrusio acetabuli was noted in only one of the control patients, and although there was no clinical evidence to support the impression, the radiological appearances were very suggestive of a previous inflammatory arthritis (Murray, 1965). This abnormality occurred in 60 hip joints of patients affected by Paget's disease, 12 patients having a bilateral abnormality. In most of the patients the associated degenerative changes were classified as minimal, and in only seven patients were more advanced degenerative changes visible. We therefore consider that this abnormality is also a feature of the Paget's process, and is attributable to bone softening and deformity. It needs to be differentiated from the "brim" sign, which is usually present in patients who have Paget's disease, and which we rely upon as a differentiating point from other conditions of the pelvis accompanied by changes in the trabecular pattern.

Many authors comment on the low frequency of symptoms in patients who have hip joint changes when the bones on either side of the hip joint are affected by Paget's disease (Murray, 1965; Machtey *et al.*, 1966; Roper, 1971). This has been our experience also; the request cards of 300 patients with Paget's disease indicated that in only 27 patients were there symptoms of hip joint degeneration. There were 37 of the control patients with similar symptoms. These low figures might be due in part to failure to question the patient closely about symptoms referable to the hip joints, but even so it seems probable that, in spite of quite marked radiological changes, both groups of patients rarely suffer symptoms from joints showing radiological evidence of degeneration, and there appears to be no difference between those with, and those without, Paget's disease. However, this method of assessing symptoms cannot be considered satisfactory, and a true assessment of symptoms in relation to Paget's disease adjacent to the hip joint can probably only be established by a prospective study combining clinical and radiological examination.

Prominent trabeculation in the femoral necks was noted in a number of patients with Paget's disease, and since this might indicate a very early stage of the bone disease, patients with Paget's disease and the controls were compared for this finding. The incidence of the finding in both groups was similar, and it therefore appears that increased trabeculation is not related to later development of Paget's disease.

Arterial calcification was sought for in all our patients and in the controls, and was found to be of similar frequency in the two groups. This would seem to negate the previous impression (De Deuxchaines and Krane, 1964) that arterial disease is more common in patients who have Paget's disease, although it must be noted that arterial calcification is in fact a poor indicator of the extent and severity of arterial disease.

REFERENCES

BARKER, J. D. P., CLOUGH, P. W. L., GUYER, P. B., and GARDNER, M. J., 1977. Paget's disease of bone in 14 British towns. *British Medical Journal*, *1*, 1181–1183.

BARRY, H. C., 1973. Paget's disease of bone. *Practitioner*, *210*, 340–350.

DE DEUXCHAINES, N. C., and KRANE, S. M., 1964. Paget's disease of bone; clinical and metabolic observations. *Medicine* (*Baltimore*), *43*, 233–266.

DICKSON, D. D., CAMP, J. D., and CHORMLEY, R. K., 1945. Osteitis deformans – Paget's disease of bone. *Radiology*, *44*, 449–470.

DUBOIS, J. L., and FRANCOIS, P., 1960. Coxopathies in Paget's disease—Radio-clinical study. *Journal Belge de Medecine Physique et de Rheumatologie*, *15*, 18–29.

GRAHAM, J., and HARRIS, W. H., 1971. Paget's disease involving the hip hoint. *Journal of Bone and Joint Surgery*, *53B*, 650–659.

GUTMAN, A. B., and KASABACH, H. H., 1936. Paget's disease (osteitis deformans); analysis of 116 cases. *American Journal of Medical Science*, *191*, 361–380.

GUYER, P. B., and CLOUGH P. W. L., 1978. Some observations on Paget's disease of bone. *Clinical Radiology*, (in press).

MACHTEY, I., RODNAN, G. P., and BENEDEK, T. G., 1966. Paget's Disease of the hip joint. *The American Journal of the Medical Sciences*, *251*, 524–531.

MARSHALL, T. R., and LING, J. T., 1963. The brim sign; a new sign in Paget's disease of the pelvis. *American Journal of Roentgenology*, *90*, 1267–1270.

MURRAY, R. O., 1965. Aetiology of primary osteo-arthritis of the hip. *British Journal of Radiology*, *38*, 810–824.

O'REILLEY, T. J., and RACE, J., 1932. Osteitis deformans. *Quarterly Journal of Medicine*, *1*, 471–497.

RECORDIER, A. M., FABRE, M., and SERRATRICE, G., 1963. The re-shaping of the acetabulum; sign of the differential diagnosis between various forms of Paget's disease and bone metastases. *Marseille Medicine*, *100*, 273–5.

ROPER, B. A., 1971. Paget's disease involving the hip joint. *Clinical Orthopaedics and Related Research*, (*80*), 33–38.

SERRE, H., SIMON, L., and CLAUSTRE, J., 1963. A propos de l'attiente des hanches au cours de la goutte. *Revue du Rheumatism et des Maladies Osteoarticularies* (*Paris*), *30*, 741–746.

STEINBACH, H. L., 1961. Some roentgen features of Paget's disease. *American Journal of Roentgenology*, *86*, 950–964.

WALKO, R., 1961. The coxopathy in Paget's disease. *Annales de Radiologie* (*Paris*), *4*, 287–294.

1978, *British Journal of Radiology*, *51*, 579–583

AUGUST 1978

Renal tubular sludging of meglumine iodipamide (Biligrafin)

By J. B. Witcombe, F.R.C.R., D.C.H.*

Department of Radiology, Red Cross War Memorial Children's Hospital, Rondebosch 7700, Cape Town, South Africa

(*Received August, 1977*)

ABSTRACT

Linear densities which were thought to represent meglumine iodipamide were seen in the renal papillary tubules of three patients for respectively four, six and nine days following intravenous cholangiography (IVC). All three patients were children with hepato-biliary disease. Two patients had biliary roundworm infestation, and one patient had hepatic dysfunction and intestinal ascariasis with possible biliary involvement. Haematuria and renal enlargement were seen in one patient, but the cholangiogram was not conclusively implicated as a cause. This renal tubular "sludging" of biliary contrast medium is recorded because of its potential nephrotoxic significance. The possible causes are discussed.

Iodipamide is partly excreted by the kidney and is often seen in the renal collecting system during intravenous cholangiography (IVC). Biliary contrast medium has not previously been observed in the renal tubules. This report concerns three cases in which linear densities were present in the renal papillae for several days after IVC. The papillary densities were not seen on the IVC films, but were first noted five hours, 24 hours, and four days respectively after contrast medium injection.

Ascaris lumbricoides infection is endemic in Cape Town and biliary ascariasis is a common cause of abdominal colic in childhood. Intravenous cholangiography usually reveals the worm in a dilated bile duct and currently over 150 cholangiograms are carried out annually at the Red Cross War Memorial Children's Hospital for this condition (Cremin and Fisher, 1976). Half of the examinations are positive. The following cases were found during a review of cholangiograms undertaken on children between 1970 and 1977.

CASE REPORTS

Case 1

A seven-year-old coloured girl presented with abdominal pain and vomiting. She weighed 20 kg which is below the twentieth percentile for her age, was anaemic and had tenderness over the liver. No jaundice or signs of dehydration were evident, but the stool contained occult blood. Initial blood tests were as follows: Hb 6.5 g-%, WBC 15000 cu. ml and ESR 50 mm/h. Radiographs of the chest and abdomen were normal and an IVC was carried out using an injection of 20 ml of 50% meglumine iodipamide (Biligrafin Forte). The IVC revealed a roundworm in the biliary tree and only a small amount of the contrast medium was seen in the kidneys (Fig. 1). Treatment was started with antihelminthics, antispasmodics, intravenous fluids, nasogastric suction and imferon injections.

One episode of macroscopic haematuria was noted the day after the IVC. A 600 c.c. blood transfusion was given in divided doses on two consecutive days. A film of the abdomen, taken the day after the IVC showed widespread linear densities in the renal papillae (Figs. 2 and 4B). Serial films taken over the next six days showed the densities becoming progressively smaller. Excretory urography was then carried out with 40 ml. of 54% sodium iothalamate (Conray 325) and this showed poor concentration of the contrast medium (Figs. 3 and 4A). The kidneys measured 12 cm in length which is five standard deviations above the mean relative to the height of her first three lumbar vertebrae (Eklöf and Ringertz, 1976). Further investigations included the following: Hb 8 g-%, blood urea 45 mg-%, sodium 136 mEq/l, potassium 4.2 mEq/l, chloride 104 mEq/l, serum creatinine 0.8 mg-%, creatinine clearance 42.5 ml, total protein 8.1 g-%, albumin 4.1 g-%, Bilirubin 0.2 mg-%, alkaline phosphatase 126 U/L (normal is less than 140), PI 100%, platelets 260000 cu. ml, complement 250 (normal

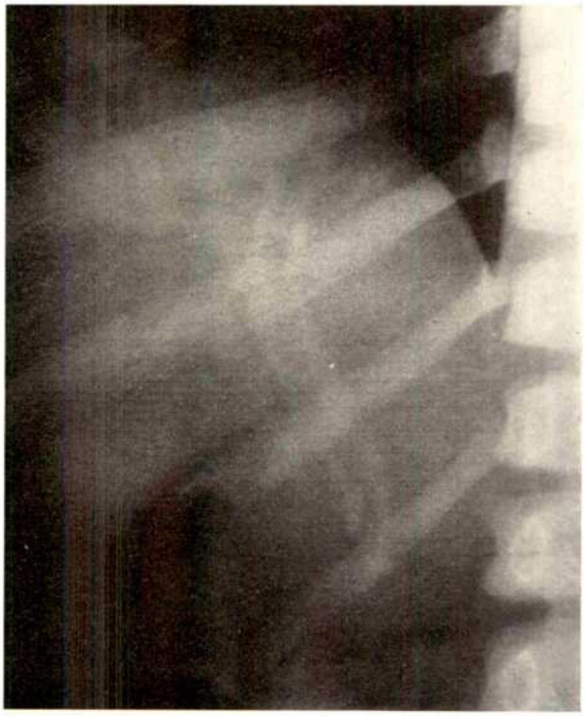


FIG. 1.

Intravenous cholangiogram. The common bile duct is dilated and a roundworm is identified as a linear filling defect, extending up the bile duct and into the left hepatic duct.

---

*Present address: Department of Radiology, The Radcliffe Infirmary, Oxford.

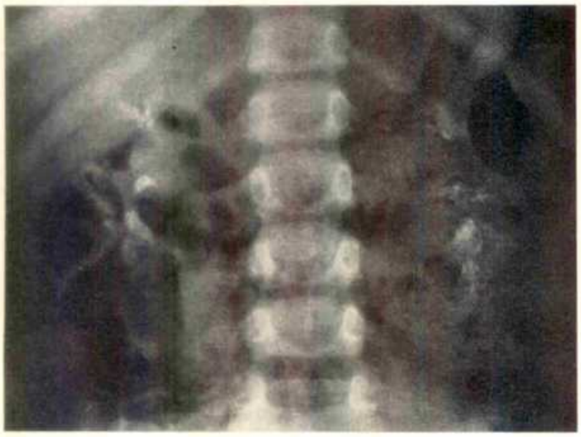


Fig. 2

Plain film of the upper abdomen showing the renal tubular opacities in Case 1.

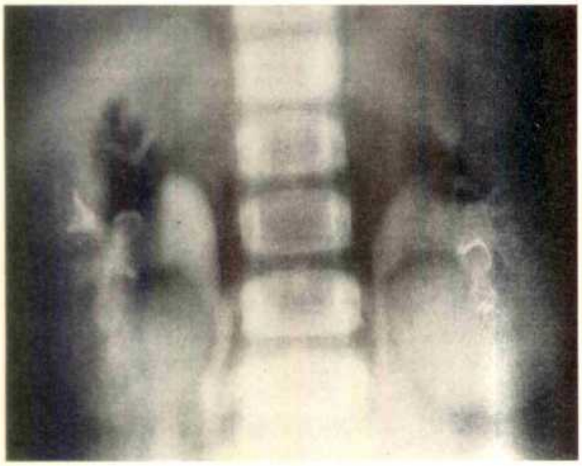


Fig. 3.

Tomogram during urography showing large kidneys in Case 1.

= 160–250), antistreptolysin titre less than 125 i.u. Repeated urine examination showed no evidence of infection, proteinuria or casts and no further haematuria was seen. Cystoscopy was negative.

When all symptoms had resolved, the patient had a repeat IVC which was normal. On this occasion no delayed renal opacification was seen.

Case 2

An eight-year-old coloured girl presented with a one-day history of peri-umbilical pain, vomiting, headache and fever. She weighed 21 kg, which is below the tenth percentile for her age, and was tender in the abdomen. Initial blood tests: Hb 14.5 g-%, WBC 10000 cu. ml, ESR. 22 ml/h, sodium 135 mEq/l, potassium 4.8 mEq/l, standard bicarbonate 18.5 mEq/l. The next day she had a swinging pyrexia and was ill, toxic and jaundiced. A repeat WBC was 4500 cu ml. The serum Bilirubin was 4.6 mg-% with 4.4 mg% conjugated, alkaline phosphatase 158 U/L, serum glutamic pyruvate transaminase 596 U/L. Ascaris and trichuris ova were present in the stools, but the following investigations were negative: chest and abdominal radiographs, liver scan, blood culture, Paul Bunnell test, Widal reaction, Australia-antigen and toxoplasma fluorescent antibody test and Tine test. The serum protein and amylase levels were within the normal range and a repeat WBC was 12400 cu ml with 18% eosinophils. Abdominal tenderness became a more marked feature and was mainly epigastric.

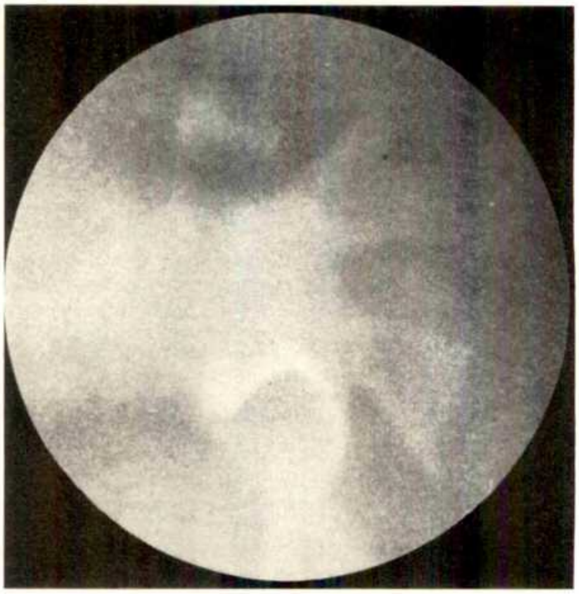


Fig. 4a.

An enlarged view of the left lower renal collecting system shown in Fig. 3.

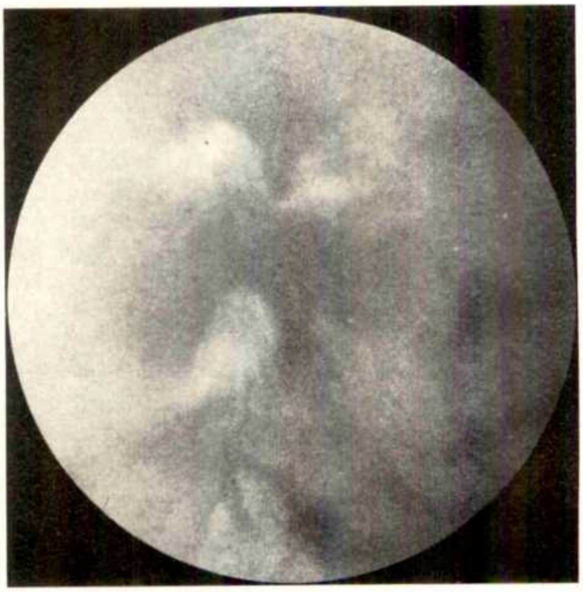


Fig. 4b.

An enlarged view of the corresponding part of Fig. 2, illustrating the relationship of the renal densities to their adjacent calyces.

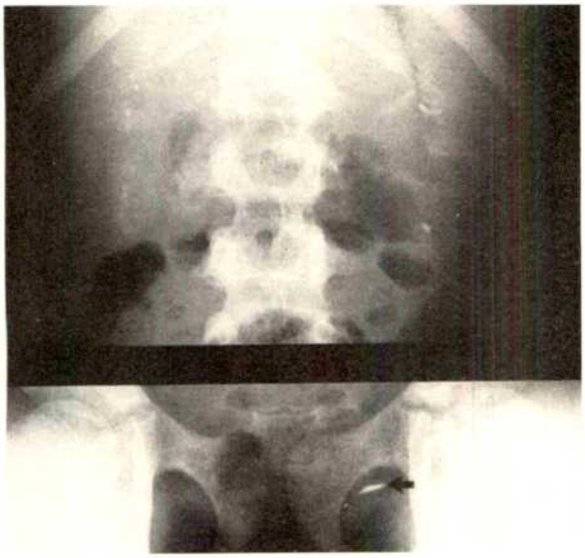


FIG. 5.

Plain films showing the renal opacities and the linear opacity (arrowed) in the base of the bladder in Case 2.

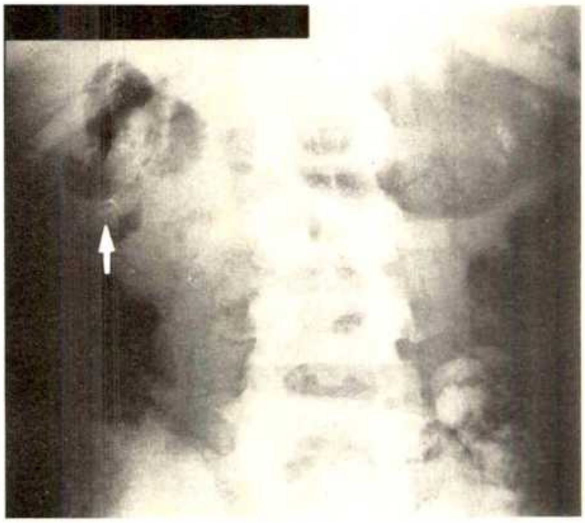


FIG. 6A.

Plain film of the abdomen in Case 3 showing linear renal papillary densities best seen in the right lower pole papilla (arrowed). Residual iodipamide is also seen in the large bowel.

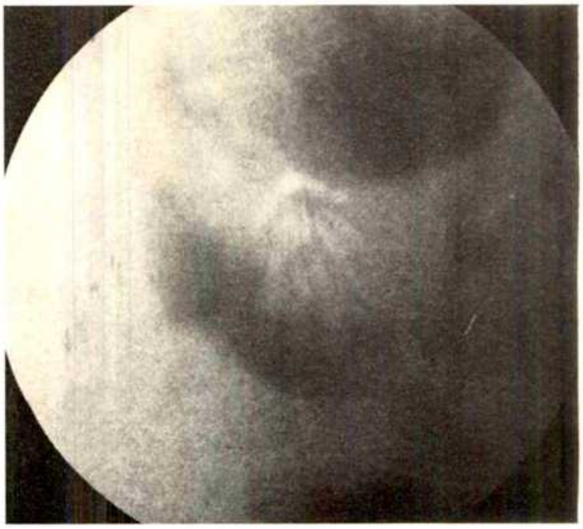


FIG. 6B.

Enlarged view of the right lower pole papilla showing the tubular densities radiating from the adjacent calyx.

An IVC was performed with a direct injection of 20 ml of Biligrafin Forte. No visualization of the biliary tree was seen and only a small amount of contrast medium was visualized in the renal pelvis. The following treatment regimen was instituted: intravenous fluids, penicillin, gentamycin, flagyl, mycostatin and antihelminthics. The patient gradually improved, but abdominal pain was a continuing problem. An abdominal radiograph taken six hours after the IVC injection, showed an appearance resembling nephrocalcinosis (Fig. 5). A thin linear density presumed to be due to contrast medium in the base of the bladder was also seen on an erect view. The renal opacities became progressively less striking over the next nine days and the bladder opacity was not seen again. Two days after the IVC, excretory urography was carried out using 40 ml of 54% sodium iothalamate (Conray 325). Contrast medium excretion was poor and the kidneys both measured 11 cm in length. (This is two standard deviations above the mean relative to the height of her first three lumbar vertebrae.) The blood urea was 29 mg-% and the serum creatinine was 1.0 mg-%. Many worms were passed in the stool and the liver function tests and temperature returned to normal. Prior to discharge two weeks later a repeat IVC was done. This showed a normal biliary tree and no delayed renal excretion of contrast medium was seen.

Case 3

A seven-year-old coloured male who weighed 25 kg, which is on the seventy-fifth percentile for his age, presented with a short history of abdominal pain and of vomiting up worms. The only abnormal finding was tenderness of the liver. Blood tests were as follows: Hb 12 g-%, WBC 12000 cu. ml, Bilirubin 1.2 mg-% with 0.4 mg% conjugated, serum protein 7.6 g-% with normal electrophoresis, serum glutamic pyruvate transaminase 85 U/L, alkaline phosphatase 208 U/L and serum amylase 180 i.u./l (normal is 70–300). Chest and abdominal radiographs were normal. An IVC was carried out with a direct injection of 20 ml of Biligrafin Forte. A worm was demonstrated in the bile duct and a small amount of contrast medium was seen in the renal pelvis. The patient improved on medical treatment, but an abdominal radiograph four days after the IVC showed linear densities in the renal papillae (Fig. 6). A follow-up IVC film done eight days later showed that the worm was still present. Delayed renal excretion of contrast was not seen following the second IVC and no adverse effects were noted after either examination.

DISCUSSION

The opacities in all three reported cases had a high radiodensity, a close relationship to the papillary tubules and a marked resemblance to medullary nephrocalcinosis. All three cases had evidence of partial biliary obstruction by ascaris lumbricoides and were given large doses of Biligrafin by relatively rapid injection; it is believed that all the injections were given over 3–5 min. Marked renal excretion was not seen on the IVC films and repeat cholangiography by the same method did not produce renal densities in any of the cases. Renal enlargement was seen in one case, in another case the kidneys were at the upper limit of the normal range and an IVP was not carried out on the third case. The opacities were not seen on any of the IVC films, but their appearance shortly after an IVC and their persistance for up to nine days is highly suggestive of tubular sludging of Biligrafin or of a complex containing Biligrafin.

The deposition of a complex of Biligrafin raises questions about its solubility. Usually less than 20% of cholangiographic medium is excreted by the kidney, but there is a wide variation and some patients have excreted up to 80% of Bilivistan through the urinary tract (Herms, 1970). The proportion of renal excretion is increased in the presence of hepatobiliary disease or when contrast medium is delivered either rapidly or in large doses (Fischer, 1965). However Biligrafin is highly soluble and it is unlikely that its solubility could be exceeded in patients so that simple crystallization could occur in the kidneys. For example, if one could succeed in concentrating contrast medium so that 100 mg of iodine were concentrated in each millilitre of urine, Biligrafin would still be soluble even at a pH of 3 (Schering, 1977). In addition even with a high dosage of Biligrafin, no solid contrast medium has been identified in the kidneys of test animals.

Biligrafin has pharmacological actions on both the renal tubules and the renal blood vessels. The tubular effects include a uricosuric action (Mudge, 1971) and Biligrafin will also reduce water clearance (Sargent *et al.*, 1973). Tubular obstruction by uric acid crystals has been suggested as a cause of nephrotoxicity following biliary radiology (Mudge., 1971). If tubular blockage had occurred in the reported cases, it could have led to a high tubular concentration of Biligrafin. However tubular obstruction by uric acid is not a common condition even in patients with hyperuricaemia given potent uricosurics. We have been unable to find any report of uric acid crystalluria following cholangiography, nor did crystalluria occur when dogs were given very high doses of cholecystographic media (Fink *et al.*, 1964). Renal tubular obstruction by uric acid is therefore an unlikely explanation for the sludging of Biligrafin.

The vascular effects of iodipamide are relevant to a discussion of the cause of renal tubular sludging. Aggregation of red cells in conjunctival vessels, (Lindgren *et al.*, 1964), hypotension (Saltzman and Sundström., 1960) and increase in renal size (Lindgren *et al.*, 1966) have been observed in patients during IVC. Rapid injection of iodipamide into animals can reduce renal blood flow and cause renal oedema (Lindgren *et al.*, 1966). Direct topical application of iodipamide to vessels not only reduces blood flow, but also causes damage to endothelium which leads to increased permeability of the vessel wall (Brånemark *et al.*, 1969). Changes in white blood cell membrane permeability and red blood cell integrity have also been reported (Lasser, 1971).

It is clear that the renal effects of biliary contrast media may be profound and indeed renal failure has been reported after cholecystography (Setter *et al.*, 1963) and cholangiography (Craft and Swales, 1967; McEvoy *et al.*, 1970). Renal injury is more likely in the presence of jaundice or biliary obstruction (Fink *et al.*, 1964; Brånemark *et al.*, 1969) and crystals have been reported in and around the renal tubules of some patients dying of renal failure after cholecystography (Setter *et al.*, 1963). The exact nature of these crystals was not established, although they were not uric acid and appeared to contain calcium.

The possibility that renal tubular sludging could be a manifestation of a renal toxic effect must now be considered. Iodipamide may cause renal tubular damage and it is possible that increased permeability of the tubular cell or basement membrane could occur without evidence of frank renal failure. Mixing of cellular or interstitial protein with urinary Biligrafin could then result in deposition of a protein-iodipamide complex in or around the collecting tubules. It is known that iodipamide binds to serum albumin (Lasser, 1971) and that globulins, IgM paraproteins and Bence-Jones proteins are precipitated by meglumine iodipamide (Lasser *et al.*, 1966). The high concentration and low pH of urine in the distal tubule would favour protein precipitation at this site and the delay in the development of the tubular opacities reported here could be explained by such a sequence of events. The haematuria and renal enlargement in our first case suggests that a renal disorder was either present or induced by the IVC and the severe anaemia in this case may have been a contributory factor causing papillary damage. However no casts or proteinuria were identified in our cases, so this mechanism remains unconfirmed.

The theory of deposition of an iodipamide-protein complex leads to consideration of whether Tamm-Horsfall protein could play a role. Tamm-Horsfall protein is a mucoprotein manufactured in the proximal nephrons and normally found in the urine. Dehydration or hypertonic infusions will concentrate Tamm-Horsfall protein in the collecting tubules where it can form a viscid gel and cause tubular blockage. Cases have been described where this occurred during excretory urography in children, resulting in oliguria and in prolonged nephrograms (Berdon *et al.*, 1969). Recovery was associated with diuresis, proteinuria and abundant urinary casts. Such a picture is not like the cases reported here, but cholangiographic media will concentrate Tamm-Horsfall protein in the urine and iodipamide will bind to protein more readily than urographic agents so that a complex containing iodipamide plus Tamm-Horsfall protein may be a possibility.

Ascaris infection was present in all three reported cases and caused hepatobiliary dysfunction. However it is difficult to postulate a more direct way in which ascariasis could cause the renal densities unless the infection had some ill-defined role on the serum protein spectrum.

Whatever the cause, our cases illustrate that renal tubular sludging of iodipamide can occur and it is the purpose of this paper to alert radiologists to the possibility. It is hoped that if further cases of tubular sludging present, their recognition and immediate investigation will help establish the cause of this phenomenon.

It appears sensible to try to avoid the stasis of contrast medium which occurs with renal tubular sludging. The cases reported here, serve to emphasize again that when carrying out an IVC, low dosage, slow delivery of contrast medium and adequate hydration of the patient are important, particularly in the presence of renal or hepatic dysfunction.

Acknowledgments

The valuable advice of Professor B. J. Cremin (Department of Radiology) and Professor P. I. Folb (Department of Pharmacology) of the University of Cape Town, and the kind assistance of Dr. A. Becker of Berlimed Pharmaceuticals (for Schering A G) and Mrs. B. Skinner (secretary) are gratefully acknowledged.

REFERENCES

Berdon, W. E., Schwartz, R. H., Becker, J., and Baker, D. H., 1969. Tamm-Horsfall proteinuria. *Radiology*, *92*, 714–722.

Brånemark, P.-I., Jacobsson, B., and Sörensen, S. E., 1969. Microvascular effects of topically applied contrast media. *Acta Radiologica* (*Diagn.*), *8*, 547–559.

Craft, I. L., and Swales, J. D., 1967. Renal failure after cholangiography. *British Medical Journal*, *2*, 736–738.

Cremin, B. J., and Fisher, R. M., 1976. Biliary ascariasis in children. *American Journal of Roentgenology*, *126*, 352–357.

Eklöf, O., and Ringertz, H., 1976. Kidney size in children —a method of assessment. *Acta Radiologica* (*Diagn.*), *17*, 617–625.

Fink, H. E., Roenigk, W. J., and Wilson, G. P., 1964. An experimental investigation of the nephrotoxic effects of oral cholecystographic agents. *American Journal of Medical Science*, *247*, 201–216.

Fischer, H. W., 1965. The excretion of iodipamide. *Radiology*, *84*, 483–491.

Herms, H. J., 1970. Excretory pathways for contrast media. *Investigative Radiology*, *5*, 490.

Lasser, E. C., 1971. Metabolic basis of contrast material toxicity—status 1971. *American Journal of Roentgenology*, *113*, 415–422.

Lasser, E. C., Lang, J. H., and Zawaszki, Z. A., 1966. Contrast media: myeloma protein precipitates in urography. *Journal of American Medical Association*, *198*, 945–947.

Lindgren, P., Löfström, B., and Saltzman, G.-F., 1964. Intravascular erythorocyte aggregation after intravenous injection of contrast media. *Acta Radiologica* (*Diagn.*), *2*, 334–343.

Lindgren, P., Nordenstam, A., and Saltzman, G.-F., 1966. Effects of iodipamide on the kidneys. *Acta Radiologica* (*Diagn.*), *4*, 129–138.

McEvoy, J., McGeown, M. G., and Kumar, R., 1970. Renal failure after radiological contrast media. *British Medical Journal*, *4*, 717–718.

Mudge, G. H., 1971. Uricosuric action of cholecystographic media. *New English Journal of Medicine*, *284*, 929–933.

Saltzman, G.-F., and Sundström, K.-A., 1960. The influence of different contrast media for cholegraphy on blood pressure and pulse rate. *Acta Radiologica* (*Diagn.*), *54*, 353–364.

Sargent, E. N., Barbour, B. H., Espinosa, N., and Meyers, H. I., 1973. Evaluation of renal function following double dose infusion intravenous cholangiography. *American Journal of Roentgenology*, *117*, 412–418.

Schering AG, 1977. Personal communication.

Setter, J. G., Maher, J. F., and Schreiner, G. E., 1963. Acute renal failure following cholecystography. *Journal of American Medical Association*, *184*, 116–124.

COLLEGE OF MEDICINE
LIBRARY

1978, *British Journal of Radiology*, *51*, 584–588

The early development of the human skeleton: a radiographic study of fetuses impregnated with silver nitrate

By B. J. Cremin, F.R.C.R., F.R.A.C.R., R. M. Fisher, D.M.R.D., and T. J. Hochschild, D.C.R.
Department of Radiology, Red Cross Children's Hospital and University of Cape Town, South Africa

(*Received January, 1978*)

ABSTRACT

The use of a silver nitrate impregnation technique and radiography for delineation of the bones of the developing skeleton is not widely known. Using this method, a study of skeleton development was undertaken over a three-year period and special attention was paid to 20 fetuses under the age of 16 weeks. The dates at which ossification in cartilage occurred and the sequence of bone development were noted. Although the technique may be used to delineate skeletal dysplasias in the stillborn, it is best suited to fetuses aged 9–20 weeks. It may become possible to show the earliest age at which bone dysplasias affect the skeleton though this is speculative at the moment.

Our initial interest in the development of the fetal skeleton was to ascertain the earliest stage at which bone and in particular, vertebral abnormalities, could be detected radiologically. Sixty-one abortions and still-births, ranging from six to 36 weeks were radiographed at the Red Cross Children's Hospital in the three-year period between 1975 and 1977. In the 20 cases under the age of 16 weeks only one bony abnormality, a thoracic hemivertebra, was found, and in these specimens the skeletal visualization was enhanced by immersion of the fetuses in a silver nitrate solution before the radiographic studies. This group forms the body of this report which records the earliest ages at which bone developed in the cartilage anlage and the order of sequential ossification.

METHODS

Opportunities for doing extensive studies on dead specimens are rare (Flecker, 1942) and there was considerable difficulty in obtaining suitable early fetuses, as many abortions are nowadays performed by a suction technique which macerates the fetus. Twenty undamaged fetuses of 16 weeks or less were obtained for study. Their ages were calculated by crown-rump and foot length measurements (Streeter 1920). This was done either on the actual specimen before fixation or from radiographs in which magnification factors had been eliminated.

The specimens were preserved in 10% formalin for 48 hours, then washed in distilled water and further immersed in 0.5% (volumetric) aqueous solution of silver nitrate for an average of five days. Frontal and lateral radiographs were then taken at a focal film distance of 110 cm, with a focal spot of 0.6 mm at 35 kV and 60–100 mA, using fine grain non-screen film.

MATERIAL

The smallest specimen in the 20 fetuses under the age of 16 weeks was estimated to be aged six weeks. No ossification was seen even after immersion in silver nitrate solution for ten days. Ossification was seen in the remaining 19 specimens and six of these have been selected to show ossification in the axial

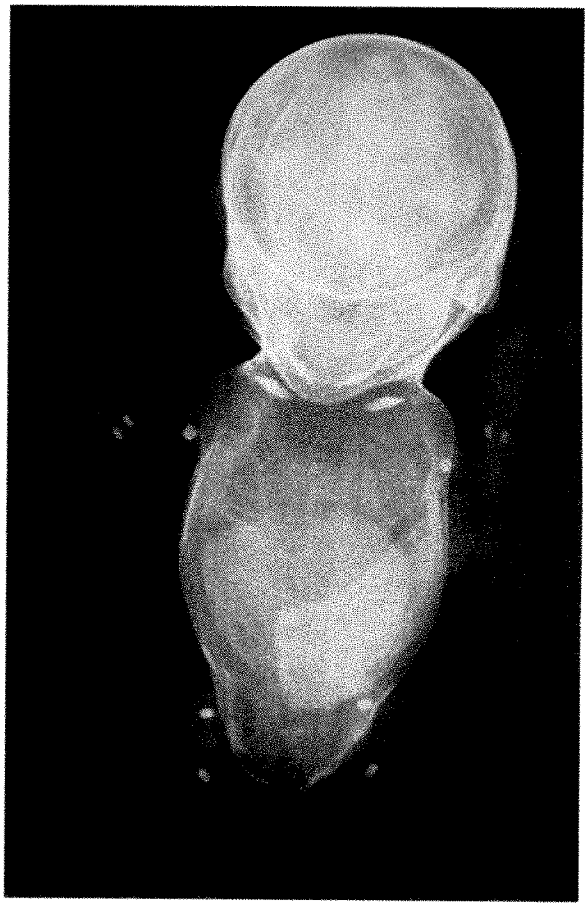


FIG. 1. *Case 1*.
Female, 29 mm (8–9 weeks) showing early development of clavicle, limb and mandible.

and appendicular skeleton. Comments on the development of the skull have largely been avoided as there was not enough undamaged material to allow a comprehensive assessment.

CASE REPORTS

Case 1

A fetus aged between eight and nine weeks demonstrated the earliest evidence of bone formation in the skeleton (Fig. 1). The order of appearances, as judged by the bone size, appeared to be clavicle, followed by upper limb (humerus, radius and ulna) and lower limb (femur and tibia). In the skull the mandible was well represented at this stage.

Case 2

A fetus aged between 10 and 11 weeks (Fig. 2). In addition to the previous mentioned centres the fetus now showed well-developed upper and lower limbs. The distal phalanges of hands and the three middle metacarpals had appeared and in the legs the fibulae were present. The first 11 ribs are well developed and the scapulae and the iliac bones had commenced ossification. In the skull the maxilla, sphenoid centres and lower squama of the occipital bone had also appeared.

Case 3

A fetus aged between 11 and 12 weeks (Fig. 3). The vertebral column makes its appearance as a pair of neural arch centres commencing in the cervical region and proceeding to develop caudally. Additional bones noted were the 12th ribs, the second to fifth metacarpals, the proximal phalanges of the second and third digits of the hand, the second and third metatarsals and distal phalanges of the first, second, third and fourth digits in the foot.

Case 4

A fetus aged 12 weeks (Fig. 4). This case is shown for comparison with the stained fetuses. The bones are discernible but lack the clarity of the stained specimens. The additional features at this age were the appearance of centres for the vertebral bodies which commenced initially in the upper lumbar region before developing in cranial and caudal directions.

Case 5

A fetus aged 13 weeks (Fig. 5). The hand showed full development of its metacarpals and the proximal and distal phalanges. In the foot the metatarsals had also fully appeared. In the spine the neural arch centres were now all

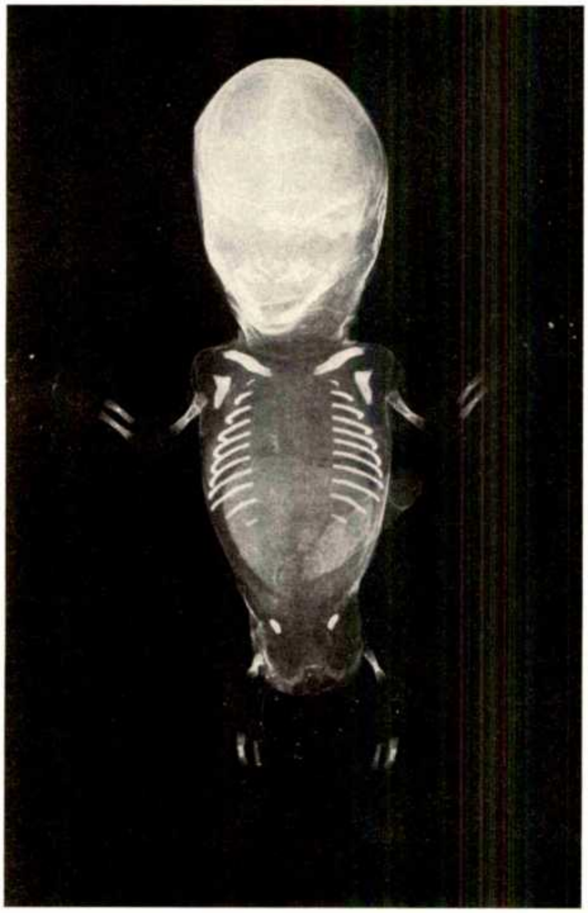


FIG. 2. *Case 2.*

Male, 45 mm (10–11 weeks) upper limbs and ribs are now well developed and the centres for the base of the skull have appeared.

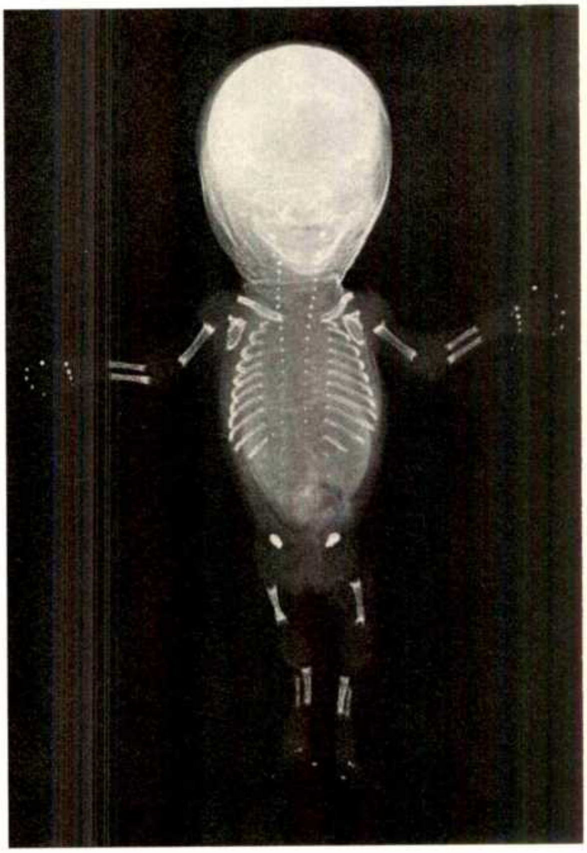


FIG. 3. *Case 3.*

Male, 55 mm (11–12 weeks). Paired centres for the neural arches appear and develop in a caudal direction.

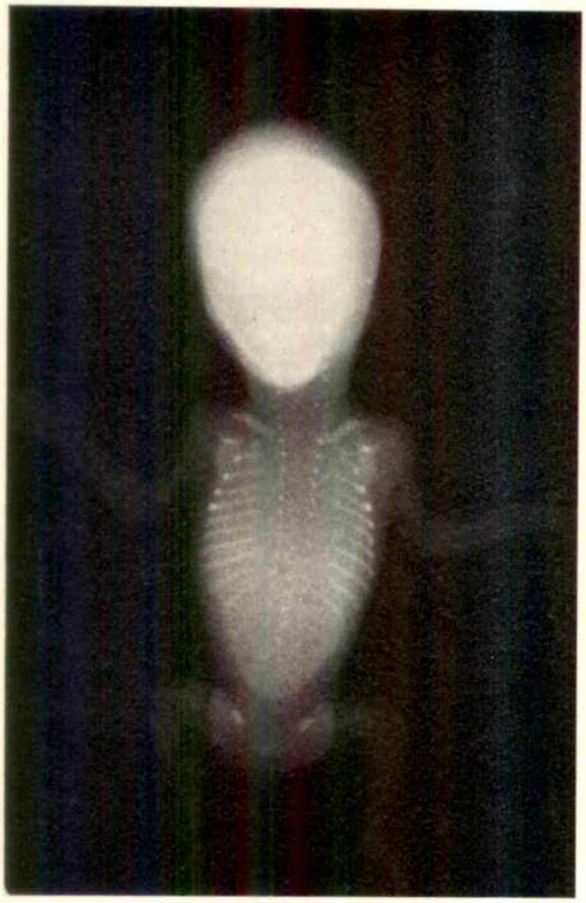


FIG. 4. *Case 4.*
Male, 62 mm (12 weeks). Unstained fetus for comparison with Fig. 5.

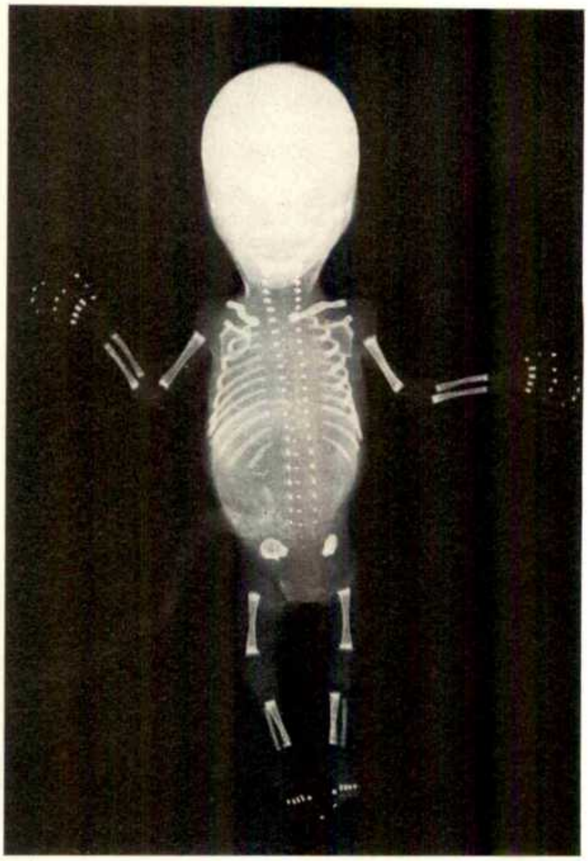


FIG. 5. *Case 5.*
Female, 75 mm (13 weeks). Ossification of vertebral bodies has commenced in thoraco-lumbar region and develops cranio-caudally.

well developed and the vertebral bodies had appeared in the upper lumbar and lower thoracic regions.

Case 6

A fetus aged 16 weeks (Figs. 6a, b, c). The appendicular and axial skeleton are now well developed. The middle phalanges in the hand and the proximal phalanges in the foot became ossified. The first round bone, the calcaneus, appeared in the foot.

DISCUSSION

Early methods for studying the development of the human skeleton were by serial sectioning of embryos and fetuses which had been stained to distinguish cartilage and bone formation. This was a laborious process and other methods arose from the investigation of the properties of staining materials which had an affinity for calcium deposits or ossification centres.

The first method was a histological one using alizarin red for staining (Noback and Robertson, 1951). The specimen is rendered transparent and the developing bones are visualized by clearing the soft tissues with potassium hydroxide or toluene. Although this method allows study in three dimensions the progress of limb, vertebral and costal skeletal development is best shown by radiographic means.

The second method, a radiographic one (Flecker, 1942) is greatly enhanced by the impregnation of the bone by heavy metal salts (Hodges, 1953; O'Rahilly and Meyer, 1956). 0.5% silver nitrate is ideal for this and it is presumed that the silver cations of the solution combine with the phosphate anion of the developing bone in the cartilage anlage.

During the period of growth under study the fetus has its most rapid proportional increase in body weight, this being by an increment of 6% a day (Usher and McLean, 1974). The development of the fetal skeleton commenced with the rapid ossification of mandible, upper limbs and thoracic cage. These

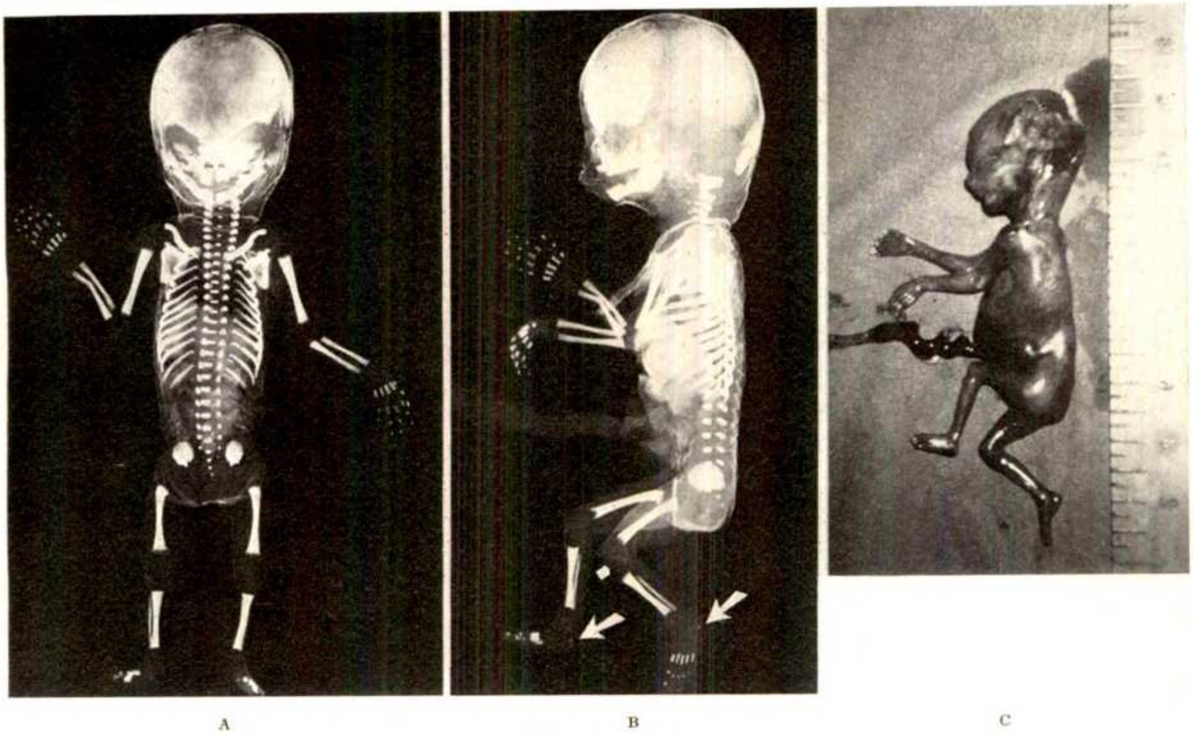


FIG. 6. *Case 6.*

(A, B). Male, 115 mm (16 weeks). Advanced development of the skeleton with first appearance of calcaneus (arrow) in foot. (C) Photograph of unfixed specimen and ruler for measuring crown-rump length.

are the centres which have an early use in the newborn infant. The spine showed a definite sequence of development, ossification commencing in the cervical neural arches and proceeding in a caudal fashion with the vertebral bodies later developing from the opposite direction.

It is possible to state the order of development of the normal skeleton with reasonable accuracy but the link between the fetal age or size with these successive stages of development is not reliable. This arises from two unavoidable sources of error. Firstly, gestation age is difficult to state with accuracy and is only broadly linked to measurements of the size of the fetus. Secondly, the rate of development of different individuals may vary within wide limits, so that it is not easy to detect a significant retardation or acceleration in the developmental processes (Streeter, 1951).

At the present state of radiography the study of the development of the human skeleton is mainly of academic interest. However, with the rapid development of new forms of imaging it may be possible to delineate at an earlier stage the appearance of the fetus. The noting that the calcaneus develops between 15 and 16 weeks rather than at 26 weeks (Hartley, 1957) as is shown by present-day pre-natal radiography may become of importance.

The second benefit of the study is to make more widely known the advantages of silver staining of fetuses. Radiography has been used in the detection of skeletal dysplasias in still-born infants (Ryan and Kozlowski, 1971). This staining method may be used to study normal variations in limb and pelvis development (Cremin, unpublished material) and at what stage skeletal abnormalities occur. The development of the clavicle at the ninth week indicates that bone dysplasias with clavicular hypoplasia such as craniocleidodysostosis involve the skeleton before that age and may even affect mesenchymal development. The early and complete ossification of phalanges and metacarpals between the 10th and 16th weeks indicates an early skeletal involvement in the many hand conditions associated with the congenital malformation syndromes (Poznanski, 1977). An absent or hypoplastic radius is associated with many congenital conditions and these studies show that its ossification is well established by at least the eighth week. Silver nitrate staining may also be used

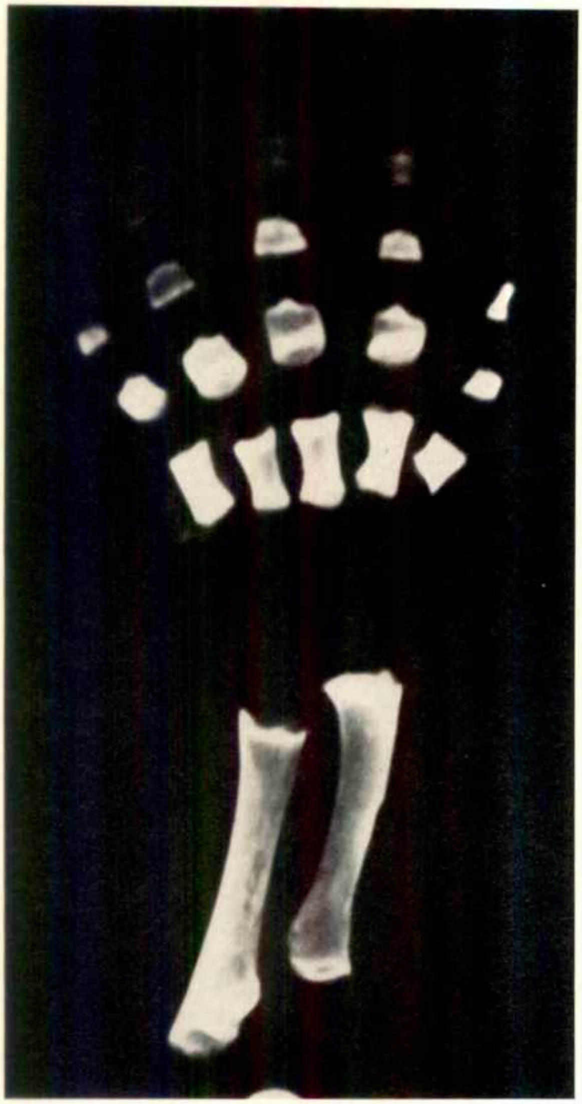


Fig. 7.

Silver nitrate stained specimen of the upper limb of a thanatophoric dwarf. The central pointing of the proximal phalanges and the configuration of the retarded growth of the small bones of the hand is typical of the condition and is well shown.

to define more clearly the small bone abnormalities in infant bone dysplasias (Fig. 7) (Cremin and Beighton, 1978). Unfortunately in fetuses that have reached the third trimester the silver nitrate solution does not easily diffuse through the skin so that prolonged immersion is required after the unpleasant task of flaying the specimen.

Acknowledgments

This study was supported by a grant from the Medical Research Council of South Africa. Our appreciation is given to Dr. M. Nelson who helped in the provision of many of the specimens and to Professor T. Keen of the Department of Anatomy who gave freely his invaluable time and advice in assessing the material and methods. The authors would also like to acknowledge Dr. H. Kaufmann of Philadelphia who first made them aware of this staining technique.

REFERENCES

Cremin, B. J., and Beighton, P., 1978. *Bone Dysplasias of Infancy* Springer Verlag, (in press).

Flecker, H., 1942. Time of appearance and fusion of ossification centers as observed by roentgenographic methods. *American Journal of Roentgenology*, *47*, 97–159.

Hartley, J. B., 1957. Radiological estimates of fetal maturity. *British Journal of Radiology*, *30*, 561–579.

Hodges, P. C., 1953. Ossification in the fetal pig: a radiographic study. *The Anatomical Record*, *116*, 315–326.

Noback, C. R., and Robertson, G. G., 1951. Sequences of appearance of ossification centers in the human skeleton during the first five prenatal months. *American Journal of Anatomy*, *89*, 1–28.

O'Rahilly, R., and Meyer, D. B., 1956. Roentgenographic investigation of the human skeleton during early fetal life. *American Journal of Roentgenology*, *76*, 455–468.

Poznanski, A. K., 1977. Approaches to the evaluation of the hand in the congenital malformation syndromes. In *Current Concepts in Pediatric Radiology*, pp. 115–126 (Springer International, Heidelberg).

Ryan, J. F., Kozlowski, K., 1971. Radiography in stillborn infants. *Australasian Radiology*, *15*, 213–226.

Streeter, G. L., 1920. Weight, sitting height, head size, foot length and menstrual age of the human embryo. *Contribution to Embryology*, *11*, Carnegie Institute of Washington, Publication No. 274, 143–170.

1951. Developmental horizons in human Embryos. *Contribution to Embryology* (*5th Issue*), *34*, 165–196.

Usher, R. H., and McLean, F. H., 1974. Normal fetal growth and the significance of fetal growth retardation. Chapter Six, *Scientific Foundation of Paediatrics*, (eds) Davis and Dobbing (Wm. Heinemann Medical Books, London).

1978, *British Journal of Radiology*, *51*, 589–595 AUGUST 1978

Pneumatosis intestinalis in children

By A. Gupta, M.B., B.S., D.M.R.D., F.F.R.R.C.S.I.*

Children's Hospital, Western Bank, Sheffield

(*Received February, 1977 and in revised form November, 1977*)

ABSTRACT

Pneumatosis intestinalis in children is a well documented condition, and is accepted as a manifestation of differing gastrointestinal tract disorders such as mechanical obstruction, vascular disturbances of the bowel with or without bacterial contamination. However, the total spectrum of the mechanisms of production of pneumatosis is not yet fully understood. The presence of pneumatosis in necrotizing enterocolitis is a very serious condition and the mortality rate is very high. Transient ischaemia in infants due to perinatal stress is considered as an important aetiological factor. Gas in the portal venous system and pneumoperitoneum are also well-known associations. Gross peritonitis and perforation of the bowel are regarded as an indication for urgent surgery. Pneumatosis due to other causes follows a benign course, and does not influence the management.

Pneumatosis intestinalis is the presence of extraluminal gas in the submucosal or in the subserosal layer of the bowel wall. The purpose of this report is to discuss the various causes and related mechanisms producing PI in children. The importance of this simple radiological sign is sometimes overlooked and attention is drawn here to its significance, especially in necrotizing enterocolitis.

Radiologically, pneumatosis is usually seen as curvilinear radiolucency along the bowel wall parallel to the intraluminal bowel gas, separated by the intervening mucosa or submucosa. Sometimes, however, the gas collections appear circular as "a series of bubbles" in the bowel wall. Pneumatosis intestinalis in the neonate is submucosal instead of subserosal as in adult (Keyting *et al.*, 1961). Pneumatosis intestinalis may involve any part of the gastrointestinal tract but most commonly involves the colon and the ileo-caecal region. The stomach, the oesophagus and the duodenum are rarely involved.

Pneumatosis intestinalis is a well known finding in premature infants with necrotizing enterocolitis. It is also present in other conditions such as intestinal obstructive lesions and vascular disturbances of the bowel. Pneumatosis is not a disease in itself, but is a manifestation of underlying pathology. The significance of this simple radiological finding varies according to the underlying pathology.

MECHANISMS

A variety of mechanisms have been suggested in the literature. The mechanical and the bacterio-vascular theories are best documented and have stood up to the test of time. The former postulates a

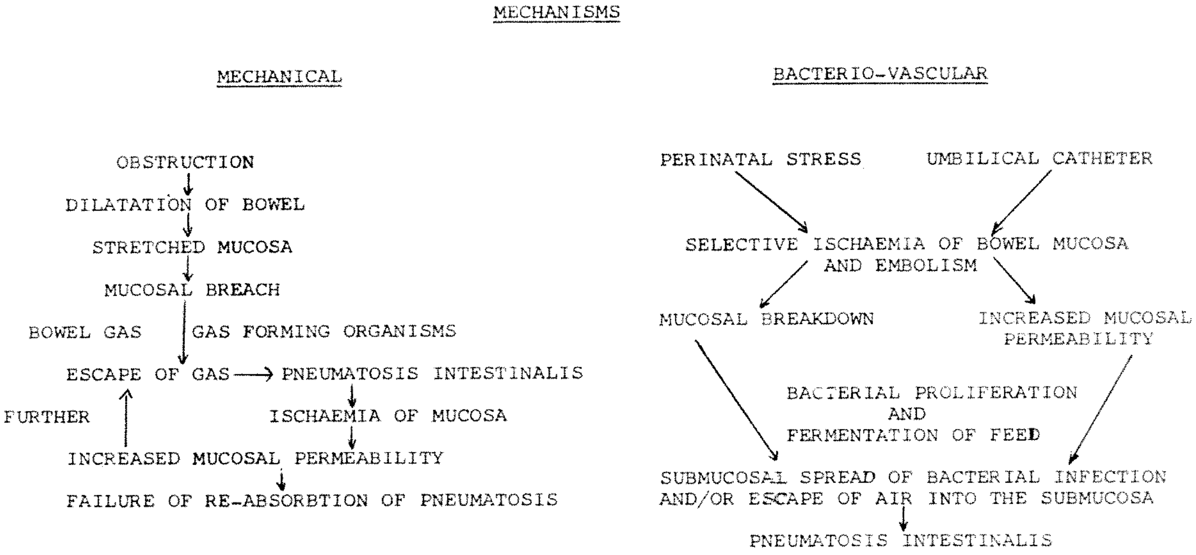

MECHANISMS
MECHANICAL
OBSTRUCTION
DILATATION OF BOWEL
STRETCHED MUCOSA
MUCOSAL BREACH
BOWEL GAS
GAS FORMING ORGANISMS
ESCAPE OF GAS
PNEUMATOSIS INTESTINALIS
FURTHER
ISCHAEMIA OF MUCOSA
INCREASED MUCOSAL PERMEABILITY
FAILURE OF RE-ABSORBTION OF PNEUMATOSIS
BACTERIO-VASCULAR
PERINATAL STRESS
UMBILICAL CATHETER
SELECTIVE ISCHAEMIA OF BOWEL MUCOSA AND EMBOLISM
MUCOSAL BREAKDOWN
INCREASED MUCOSAL PERMEABILITY
BACTERIAL PROLIFERATION AND FERMENTATION OF FEED
SUBMUCOSAL SPREAD OF BACTERIAL INFECTION AND/OR ESCAPE OF AIR INTO THE SUBMUCOSA
PNEUMATOSIS INTESTINALIS

FIG. 1

Mechanism production of pneumatosis.

---

*Present address: East India Clinic Ltd., 8/5, Alipore Road, Calcutta-27, India.

leak of intraluminal bowel gas into the submucosal layer through a breach in the bowel mucosa, whereas the latter suggests that gas forming organisms together with mucosal ischaemia are the causal agents (Fig. 1).

Mechanical

The mechanical theory is the simplest one to understand. Extraluminal bowel gas may be seen in the markedly dilated bowel from obstructive lesions such as atresia of bowel at any level, Hirschsprung's disease, or meconium ileus. There is a rise in the intraluminal pressure in the proximal bowel as a result of obstruction. With a further rise in intraluminal pressure due to peristalsis there may be a breach in the bowel mucosa. Gas may then escape from the high pressure intraluminal space to the submucosal layer. The extraluminal submucosal gas will separate the mucosa from the submucosa causing ischaemia. The ischaemia of the bowel mucosa may increase the permeability causing further diffusion of intraluminal gas into the submucosal space. There will also be failure of reabsorption of this extraluminal gas by the ischaemic bowel mucosa (Vichi *et al.*, 1973).

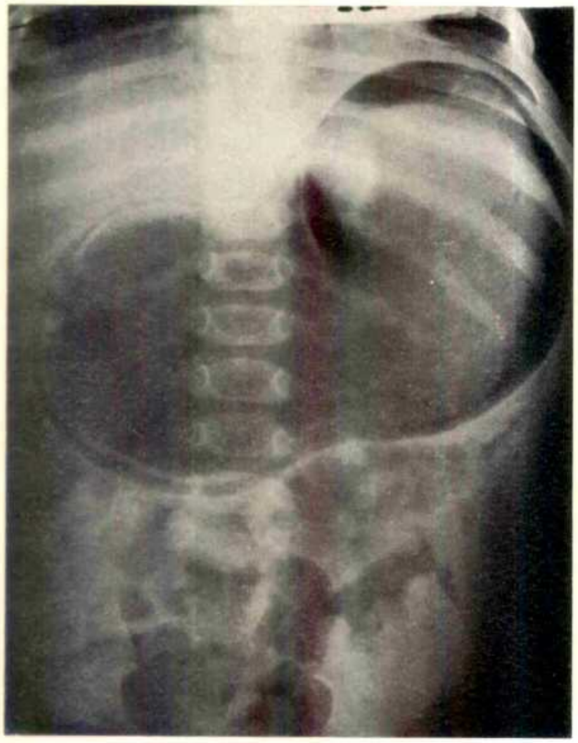


FIG. 2. *Case 1.*
Interstitial gastric emphysema.

The following three cases illustrate the mechanical theory.

Case No. 1—duodenal septum

This baby, a case of Down's syndrome, presented with vomiting (Gupta, 1977). The supine film (Fig. 2) of the abdomen demonstrates a translucent "halo" around the stomach, parallel to the intragastric bowel gas, due to the presence of interstitial gastric emphysema. At operation a tight duodenal septum with s small central aperture was found to be the cause of obstruction. Following excision of the septum, a follow-up film was taken next day, and this showed complete reabsorbtion of the pneumatosis.

Case No. 2—Hirschsprung's disease

Initially the baby was well but later presented with episodes of vomiting and constipation. The film (Fig. 3) shows a linear radiolucency in the right iliac fossa parallel to the intraluminal bowel gas in the caecum. Following this examination the child died suddenly due to aspiration of vomit. At autopsy the aganglionic segment of Hirschsprung's disease was confirmed.

Case No. 3—meconium ileus

This neonate started vomiting at eighteen hours after birth. There was no passage of meconium and abdomen was distended. The plain film (Fig. 4) shows marked bowel distension and pneumatosis; both linear and circular type of radiolucencies are present. At operation a high meconium ileus was found, meconium filling a 25 cm ileal loop.

BACTERIO-VASCULAR

Necrotizing enterocolitis is the commonest cause of PI in premature infants. This is an extremely serious clinical condition but the exact aetiological cause is uncertain. Three essential components described by Santulli *et al.* (1975) are injury to the

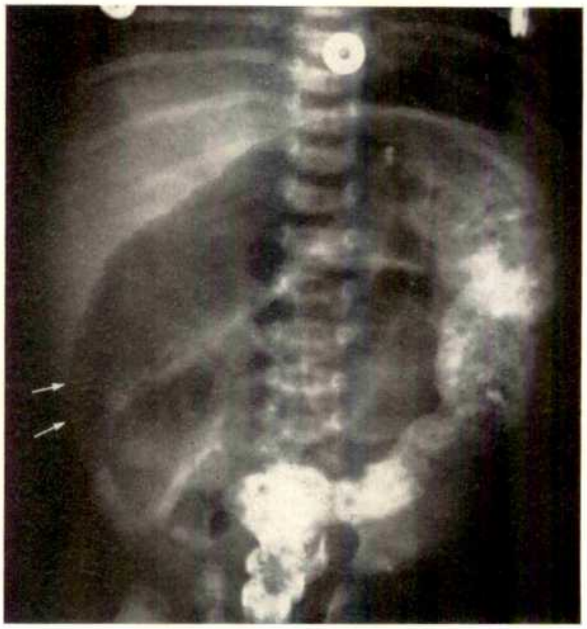


FIG. 3. *Case 2.*
Hirschsprung's disease.

intestinal mucosa, the presence of bacteria and the availability of a metabolic substrate derived from artificial feed. Injury to the intestinal mucosa is a direct result of hypoxia. Most premature infants undergo some degree of postnatal stress. Touloukian *et al.* (1972) have shown the role of hypoxia by experiments in piglets. It is suggested (Lloyd, 1969) that the redistribution of cardiac output to vital organs such as brain and heart is a stress phenomenon and there is relative ischaemia and hypoxia in the less vital organs, such as gastro-intestinal tract, limbs, etc. Intraluminal injection of gram-negative organisms have been shown to produce a pneumatosis-like picture in experimental animals (Keyting *et al.*, 1961). Klebsiella type 26 was cultured from the blood or the peritoneal fluid in six out of twelve patients with necrotizing enterocolitis by Hill *et al.* (1974). Blood culture showed gram-negative organisms in 17 infants out of 64 in the series by Santulli *et al.* (1975). These findings all support the infective mechanism. There is definite breach of mucosa due to ulceration of the bowel affected by necrotizing entercolitis. Multiple ulcerations are demonstrated both by resection and/or at autopsy (Santulli *et al.*, 1975). Infection can be spread into the bowel wall through the ulcerated mucosa and produce pneumatosis. A review at the Babies Hospital in New York (Santulli *et al.*, 1975) revealed that most infants who developed necrotizing enterocolitis had been fed prior to the onset of symptoms. Barlow *et al.* (1974) showed some remarkable findings in their experiments in rats. Breast fed animals never developed necrotizing enterocolitis even with bacterial contamination.

Necrotizing enterocolitis is also seen in infants who received exchange transfusion. Some authors suggest embolization as the initial triggering factor producing ischaemia (Corkery *et al.*, 1968). Umbilical catheterization may produce systematic hypotension. In hypoxia blood may also be shunted through, by-passing the mucosal supply. All these factors may contribute to the production of ischaemia of bowel. Bacteria may be introduced through the umbilical catheter; *Pseudomona pyocyanea* and *E. Coli* have been identified (Orme and Eades, 1968). Bacterial proliferation and the resultant endotoxin released by the bacteria may produce mucosal ulceration and pneumatosis.

Case No. 4—exchange transfusion

This neonate received an exchange transfusion for Rh. incompatability on the day of birth and a second one on the following day. Soon after the second transfusion the child passed blood stained meconium. The plain film (Fig. 5) taken at this stage shows distended bowel and pneumatosis of the left colon, presumably due to ulceration. Unfortunately the significance of this radiological finding was overlooked and a barium meal was done. A follow-up film taken next day (Fig. 6) shows an abnormal collection of barium in the left lower abdomen due to leakage of barium into the peritoneal cavity. An urgent operation was performed and necrotic colon from the hepatic flexure to the sigmoid colon was resected, but the child died shortly afterwards. An autopsy showed necrosis of the remainder of

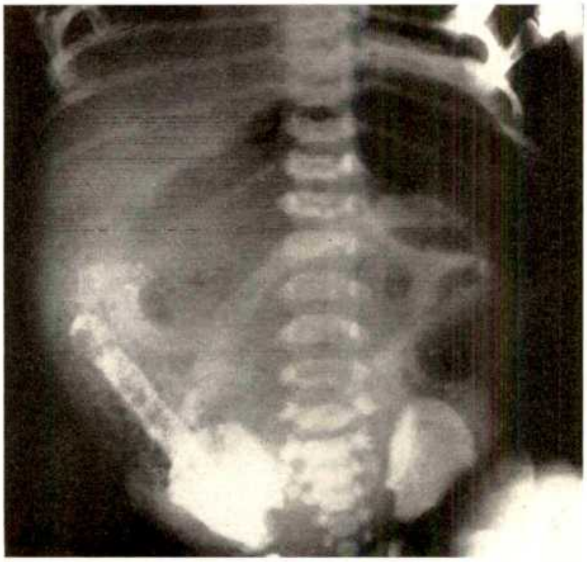


FIG. 4. *Case 3.*
Meconium ileus.

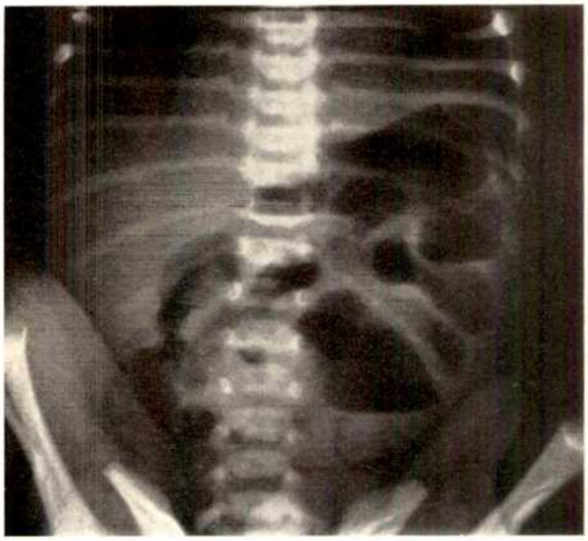


FIG. 5. *Case 4.*
Exchange transfusion.

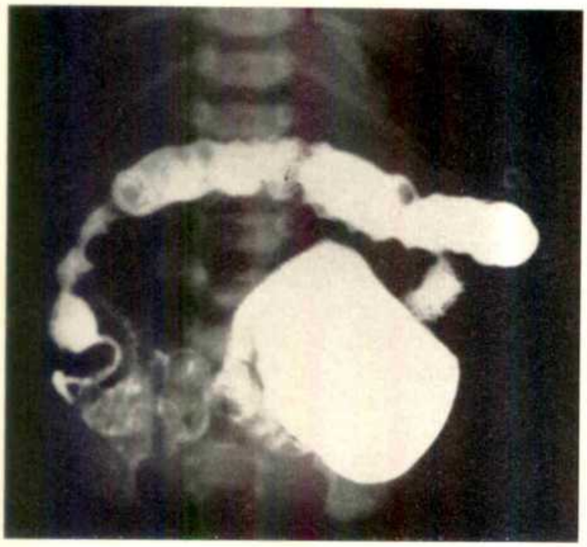


FIG. 6. *Case 4.*
Exchange transfusion.

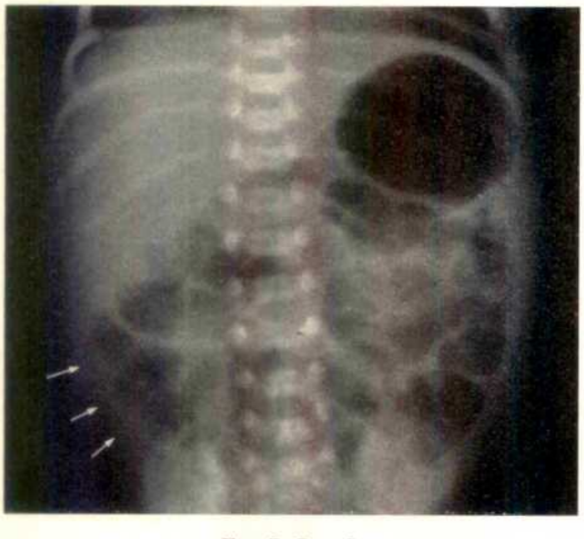


FIG. 7. *Case 5.*
Umbilical artery catheter.

the colon. There was no history or evidence of perinatal hypoxia. The baby was full term and delivered by Caesarean section. Moreover, the baby was not fed by mouth at any stage. The cause of NE here is probably the exchange transfusion and severe vascular disturbances of the bowel.

Case No. 5—umbilical artery catheter

This is a premature neonate with a birth weight of 1.5 kg suffering from respiratory distress syndrome. An umbilical artery catheter was inserted. She developed abdominal distension and also passed blood stained meconium. Plain film (Fig. 7) shows the presence of pneumatosis in the right iliac fossa. The child was treated conservatively but died after five days. An autopsy was not done.

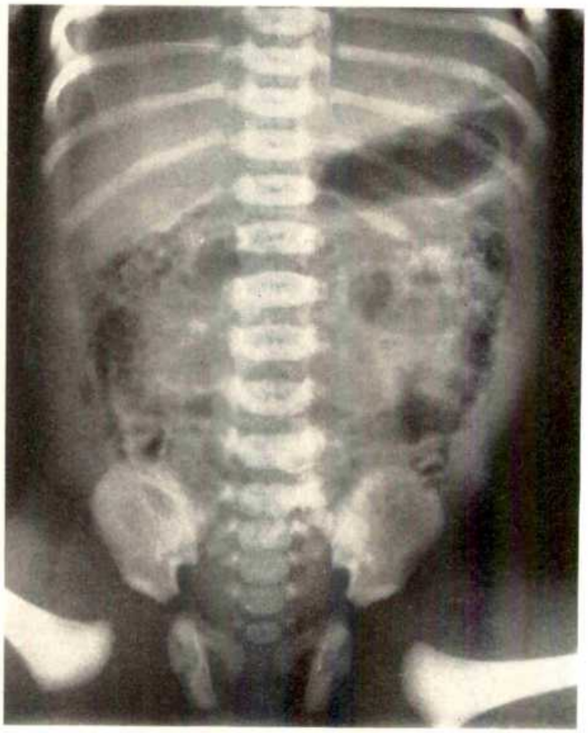


FIG. 8. *Case 6.*
Necrotizing enterocolitis.

Case No. 6—necrotizing enterocolitis

This neonate developed abdominal distension two days after birth. The plain film (Fig. 8) shows extensive pneumatosis from the right iliac fossa to the left iliac fossa. A follow-up film taken next day (Fig. 9) shows gross free peritoneal air below the diaphragms due to perforation of the bowel. The infant died shortly after this and an autopsy confirmed extensive NE involving the whole of the large bowel, and the distal ileum.

Case No. 7—necrotizing enterocolitis

This example of NE also shows gas in the portal venous system (Fig. 10) seen as linear radiolucencies in the right hypochondrium in the region of the liver. The child was treated conservatively with antibiotics. A follow-up film taken (Fig. 11) next day shows presence of free air under both diaphragms due to perforation of the affected bowel. The gas in the portal venous system is unchanged. The baby died shortly after this and an autopsy was not undertaken.

Case No. 8—colonic stricture following necrotizing enterocolitis

This child aged four months was admitted with the clinical signs of intestinal obstruction. The film (Fig. 12) shows two narrowed segments in the left colon. Four months prior to this, two days after birth, the child was admitted with the clinical diagnosis of necrotizing enterocolitis. Serial plain films of the abdomen were taken and a barium enema was also undertaken on the second day of admission. These failed to show any radiological signs of necrotizing enterocolitis. The child was treated conservatively with antibiotics. This is presented as an example of retrospective confirmation of necrotizing enterocolitis.

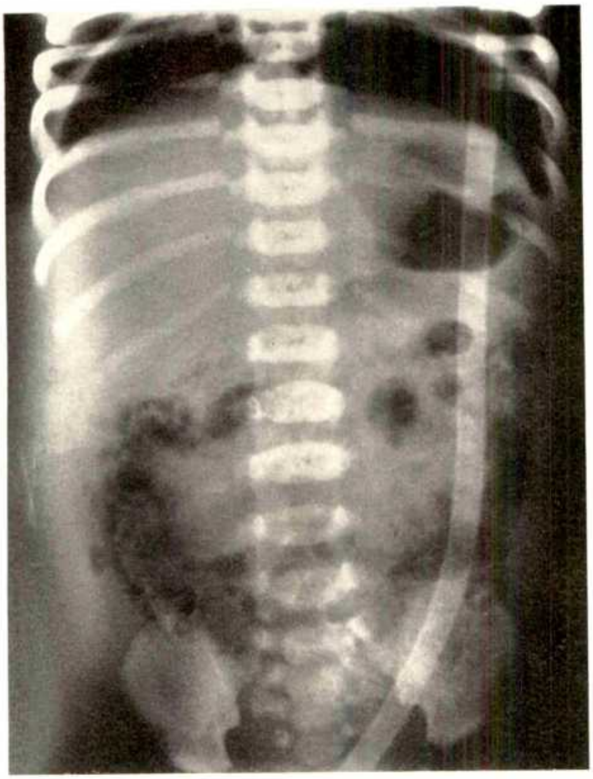


Fig. 9. *Case 6.*
Necrotizing enterocolitis.

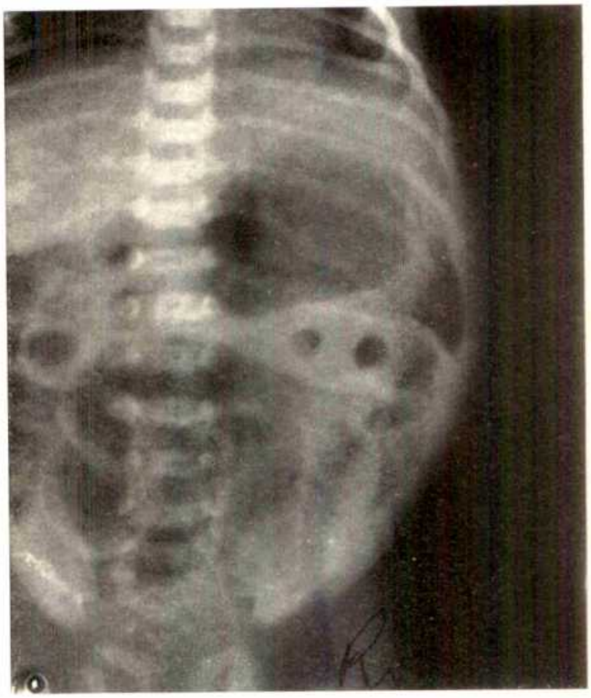


Fig. 10. *Case 7.*
Necrotizing enterocolitis with gas in the portal venous system and perforation.

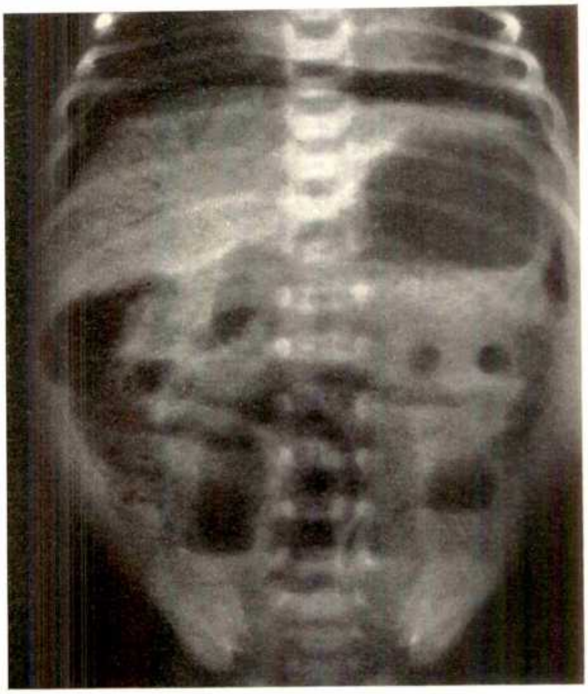


Fig. 11. *Case 7.*
Necrotizing enterocolitis with gas in the portal venous system and perforation.

Other Causes

Pneumomediastinum, instrumentation such as oesophagoscopy, sigmoidoscopy, etc., are also reported to produce pneumatosis as a rare association. In pneumomediastinum air is said to follow the aorta along the subadventitial layer into the branches in the abdomen, and eventually to the bowel wall. Examples of these in adults can be found in literature but not a single conclusive case has yet been cited in infants (Robinson *et al.*, 1974).

Steroid and immuno-suppressive treatment may also act as an aetiological factor in the development of pneumatosis in children. Borns and Johnston (1973) have reported a series where pneumatosis was found as an incidental finding in children under long-term immuno-suppressive therapy. This is thought to be due to mucosal defect in the Peyers' patches, as the hypertrophied Peyers' patches shrink with immuno-suppressive therapy. Intraluminal bowel gas may escape through this mucosal defect.

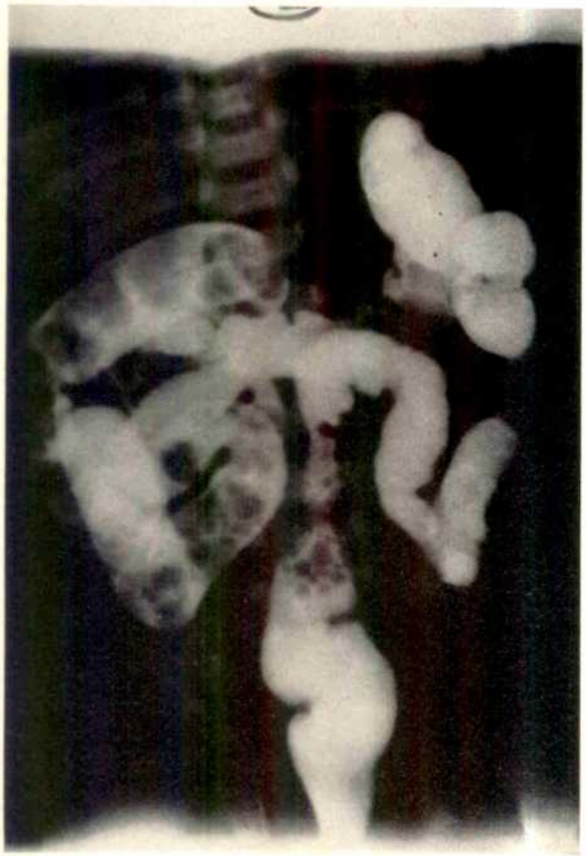


Fig. 12. *Case 8.*
Colonic strictures following necrotizing enterocolitis.

Discussion

Radiology is of extreme importance in the diagnosis and proper management of pneumatosis intestinalis in children. The radiologist should be alert for the development of pneumatosis in the non-breast fed and in the premature neonate with stress, possible sepsis and umbilical catheterization. In the infants necrotizing enterocolitis typically presents as abdominal distension, bile stained vomiting and blood in the stool. Plain abdominal films may show pneumatosis and this presents very early in the clinical course. The presence of pneumatosis intestinalis will confirm the clinical diagnosis. Further radiological investigations are often unnecessary. In fact, contrast enema studies may be dangerous, as this may cause perforation of the involved bowel segment. The plain film may also show presence of gas in the portal venous system. This was considered to be an ominous sign with bad prognosis. However, this is no longer considered to be an indication for surgery, nor does this foreshadow a fatal outcome (Leonidas *et al.*, 1973). The indications for urgent surgery are radiological evidence of free intraperitoneal air and also free intraperitoneal fluid. If the plain film is negative then contrast enema is undertaken at certain centres to demonstrate the mucosal ulceration; but this is of doubtful value as the absence of ulceration does not exclude the clinical diagnosis of necrotizing enterocolitis. In the presence of the slightest suspicion of necrotizing enterocolitis the contrast enema should be avoided and the case should be followed-up by only plain film examination. Cases are shown to improve with conservative treatment, but may present three or four months later with signs of intestinal obstruction (Corkery *et al.*, 1968). Contrast enema at this stage may reveal stricture of the bowel. The strictures are thought to be due to healing of the ulcers by fibrous tissue scars.

Pneumatosis in children due to other causes is usually an incidental radiological finding. Moreover, these children are not always seriously ill. Aetiological factors like congenital bowel atresia are usually diagnosed shortly after birth. Excision or by-pass of the underlying obstruction produce complete reabsorbtion of the pneumatosis. In meconium ileus the treatment may be by water-soluble contrast enema, and therefore, it is imperative that necrotizing enterocolitis must always be clinically excluded as it contra-indicates enema treatment. The children under long-term immuno-suppression may show PI in the routine follow-up films of the abdomen and chest as an incidental finding and this is of no clinical significance.

Conclusion

Pneumatosis intestinalis may develop due to mechanical obstruction and vascular disturbances of the bowel with or without bacterial contamination. This is also reported in children under long-term immuno-suppressive therapy.

Pneumatosis in mechanical obstruction is usually an incidental finding and bears no significant relation to its management. Similarly, pneumatosis in immuno-suppressive therapy is also an incidental finding and is of no clinical significance. Necrotizing enterocolitis is usually recognized clinically by its typical presentation of abdominal distension, bile stained vomiting and presence of blood in the stool. In presence of pneumatosis in necrotizing enterocolitis, contrast enema is contra-indicated as this may produce perforation. Plain abdominal films are sufficient to follow-up for detection of early perforation. Pneumatosis by itself or even with gas in the portal venous system is no longer regarded as indication for urgent surgery. Surgery is indicated in presence of gross peritonitis and perforation of the bowel.

ACKNOWLEDGMENTS

The author is extremely indebted and grateful to Dr. R. K. Levick, Consultant Paediatric Radiologist, Sheffield, for his constant guidance and advice throughout this project. I wish to thank Professor R. B. Zachary and Mr. L. Spitz, Consultant Paediatric Surgeon, Sheffield, for their permission to use the cases who were admitted under their care. Thanks are also due to staff of the Photographic Department, Sheffield Central District. I should like to thank my wife, Sandra, for typing all the materials during the preparation of this article.

REFERENCES

BARLOW, B., SANTULLI, T. V., HEIRD, W. C., PITT, J., BLANC, W. A., and SCHULLINGER, J. N., 1974. An experimental study of acute neonatal enterocolitis—the importance of breast milk. *Journal of Pediatric Surgery, 9*, 387–594.

BORNS, P. F., and JOHNSTON, T. A., 1973. Indolent pneumatosis of the bowel wall associated with immune suppressive therapy. *Annals de Radiologie, 16 (3–4)*, 163–166.

CORKERY, J. J., DUBOWITZ, V., LISTER, J., and MOOSA, A., 1968. Colonic perforation after exchange transfusion. *British Medical Journal, 4*, 345–347.

GUPTA, A., 1977. Interstitial gastric emphysema in a child with duodenal stenosis. *British Journal of Radiology, 50*, 222–224.

HILL, H. R., HUNT, C. E., and MATSEN, J. M., 1974. Nosocomial colonization with Klebsiella type 26 in a neonatal intensive care unit associated with an outbreak of sepsis meningitis and necrotizing enterocolitis. *The Journal of Pediatrics, 85*, 415–419.

KEYTING, W. S., MCCARVER, R. B., KOVARIK, J. L., and DAYWITT, A. L., 1961. Pneumatosis intestinalis: a new concept. *Radiology, 76*, 733–741.

LEONIDAS, J. C., KRASNA, I. H., FOX, H. A., and BRODER, M. A., 1973. Peritoneal fluid in necrotizing enterocolitis: a radiologic sign of clinical deterioration. *The Journal of Pediatrics, 82*, 672–675.

LLOYD, J. R., 1969. The etiology of gastro intestinal perforation in newborn. *The Journal of Pediatric Surgery, 4*, 77–84.

ORME, R. L'E., and EADES, S. M., 1968. Perforation of the bowel in the newborn as a complication of exchange transfusion. *British Medical Journal, 3*, 349–351.

ROBINSON, A. S., GROSSMAN, H., and BRUMLEY, G. W., 1974. Pneumatosis intestinalis in the neonate. *Radiology, 113*, 504.

SANTULLI, T. V., SCHULLINGER, J. N., HEIRD, W. C., GONGAWARE, R. D., WIGGER, J., BARLOW, B., BLANC, W. A., and BERDON, W. E., 1975. Acute necrotizing enterocolitis in infancy: a review of 64 cases, *Pediatrics, 55*, 376–387.

TOULOUKIAN, R. J., POSCH, J. N., and SPENCER, R., 1972. The pathogenesis of ischemic gastroenterocolitis of the neonate: selective gut mucosal ischemia in asphyxiated neonatal piglets. *Journal of Pediatric Surgery, 7*, 194–205.

VICHI, G. F., MAGGINI, M., MOGGI, P., GORI, F., and PAOLI, F., 1973. Pneumatosis intestinalis in infants: clinical, radiological and anatomo-pathological study on eighteen patients. *Annales De Radiologie, 16 (3–4)*, 153–163.

Book review

Radiology for Medical Students. By David Sutton, pp. vii + 153, 1977 (Edinburgh, Churchill Livingstone) £4·95.

The present and near future is and will be an exciting time to be a radiologist. A rapidly-expanding imaging technology is giving the radiologist a new, powerful range of diagnostic tools—radio-isotope imaging, ultrasound, computed tomography and the promise of NMR imaging to come. This expansion, together with the application of the disciplines of cost-effectiveness and medical auditing to radiology has led to the present reappraisal of the clinical role of the radiologist. Can medicine afford to allow the radiologist the privilege of being an informed observer only? Can the profession afford to be remote from the discussion and choice of clinical investigations? These questions are being answered and the answers are crucial to the future of the profession. It is an irony that it should be at this time of change that it is generally recognised that radiology should be taught to medical students.

Radiology for Medical Students is the third edition of a book first published in 1965 under the title Radiology for General Practitioners and Medical Students, a title retained for the second edition published in 1971. The present edition has been increased in length by a third, retaining the same number and, except for a single change in name, the same chapter headings. The chapters are well illustrated and the quality of the X-ray reproductions is high. Its origin as a series of articles is evident in the organization of the book. Each system has a chapter or chapters dedicated to it giving an account of the radiological techniques available for its examination. This type of presentation works best in those chapters where it is organized around the patho-physiology of the system, for instance the chapters on gastroenterology. The chapters have been brought up-to-date by the insertion of new material rather than by being re-written. This has led to some anomalies. In chapter eight a reference has been inserted in the present edition referring the reader to a radio-isotope lung scanning technique described in Chapter 13 of the previous but not the present edition.

Radiology for Medical Students provides an excellent introduction to the range of examinations available to the Radiologist and clinician but does not provide the clinical or technological reasons for the choice of investigation relevant to common clinical problems.

J. J. K. BEST.

1978, *British Journal of Radiology*, *51*, 596–598

Ultrasound and hepatic metastases

By F. R. Vicary,* M.B., M.R.C.P., and I. Shirley, M.B., Ch.B., D.R.C.O.G.,
Department of Ultrasound, University College Hospital, Gower Street, London, W.C.1

(*Received November, 1977*)

ABSTRACT

Recent advances in ultrasonic technology have permitted differentiation of tissue within an organ. Fifty-nine patients in whom satisfactory follow-up could be obtained underwent grey-scale ultrasonic examination of their livers. Fifty-three patients were scanned successfully and of these a correct diagnosis as to whether metastases were present or not was given in 46.

Ultrasound is a safe non-invasive way of detecting hepatic metastases.

The detection of hepatic metastases plays an important part in the management of patients with cancer.

Many techniques are available which attempt to detect tumours in the liver.

Hepatic radioisotope ^{99}Tc^{m} scanning in experienced hands has a variable accuracy. One series (Davies *et al.*, 1974) reported an overall accuracy of 95% but other series have shown less accuracy often with many false positives (Conn and Elkington, 1968; Jhingram *et al.*, 1971; Magnum and Powell, 1973). A raised serum alkaline phosphatase is often the most consistent single parameter in the detection of metastases (Smith *et al.*, 1976; Jhingram *et al.*, 1971) but obviously does not give specific information as to site, size or number of metastases.

Hepatic arteriography in experienced hands has a high pick-up rate for metastases (Freeman *et al.*, 1969). Laparoscopy with its ability to biopsy a specific hepatic lesion has been shown to be useful in the diagnosis of hepatic tumours (Etienne *et al.*, 1976).

The recent technical advance in ultrasound equipment known as grey-scaling has permitted the simultaneous display of both organ outlines and their structure. Grey-scaling permits comparison of adjacent areas of organ tissue and thus an appreciation of abnormal echo patterns.

The technical feasability of delineating tumours within the liver was shown by Taylor *et al.* (1974). They demonstrated that metastases within the liver may be more or less reflective than normal liver tissue. Recently a study of a series of patients with breast carcinoma (Smith *et al.*, 1976) suggested that ultrasound was more accurate than radioisotope scanning in detecting liver metastases. The purpose of this study was to define the accuracy in detecting the presence or absence of hepatic metastases from a wide range of primary tumours.

METHODS

Patients included in the study are all patients referred to the clinic in whom satisfactory follow-up

TABLE I

LIVER TUMOURS SCANNED WITH SATISFACTORY FOLLOW UP

Patients	59
Satisfactorily scanned	53 (31 had tumours) (22 had no tumours)
Number correct	46
(4 false negatives, 3 false positives)	

TABLE II

CRITERIA FOR FINAL CLINICAL DIAGNOSIS OF LIVER METASTASES

Either	—Laparotomy findings or liver biopsy histology
Or	—Clinical hepatomegaly and raised alkaline phosphatase often with positive ^{99}Tc scan.

TABLE III

CRITERIA FOR FINAL CLINICAL DIAGNOSIS OF NORMAL LIVER

Either	—Laparotomy
Or	—No hepatomegaly and normal alkaline phosphatase often with negative ^{99}Tc scan. Six months after ultrasound.

TABLE IV

SITE OF PRIMARY CARCINOMA

Colon	13	
Stomach	10	(2 false negative) (2 false positive)
Bronchus	9	
Pancreas	9	
Breast	3	(1 false negative)
Ovary	2	(1 false negative)
Others	7	(1 false positive)

---

*Present address: Royal Northern Hospital, Caledonian Road, London, N6.

was possible. There were 33 females and 26 males with an age range of from 37 to 88 years.

All patients were examined by one or other of the authors with a Nuclear Enterprises Diasonograph (NE4102) with grey-scale attachment. Scans were performed with the patients lying supine. The skin of the abdomen was prepared, using warm arachis oil to ensure satisfactory transmission of sound waves. Para sagittal slices at 1 cm intervals were made across the liver. Occasionally, transverse cuts were made to confirm or refute the findings of the parasagittal cuts.

The operator often knew the results of biochemical liver function tests performed on the patients being scanned. Only exceptionally was the result of radioisotope scanning known.

Results

Follow-up was possible in a total of 59 patients. In six of these patients satisfactory liver pictures were not obtained for technical reasons (usually due to excessive colonic gas preventing transmission of sound through the liver). In 46 of the 53 scanned satisfactorily, the ultrasound scan gave the correct answer (see Table I) using the clinical criteria set out in Tables II and III.

A patient was considered to have definite evidence of metastases if he had positive biopsy (taken at

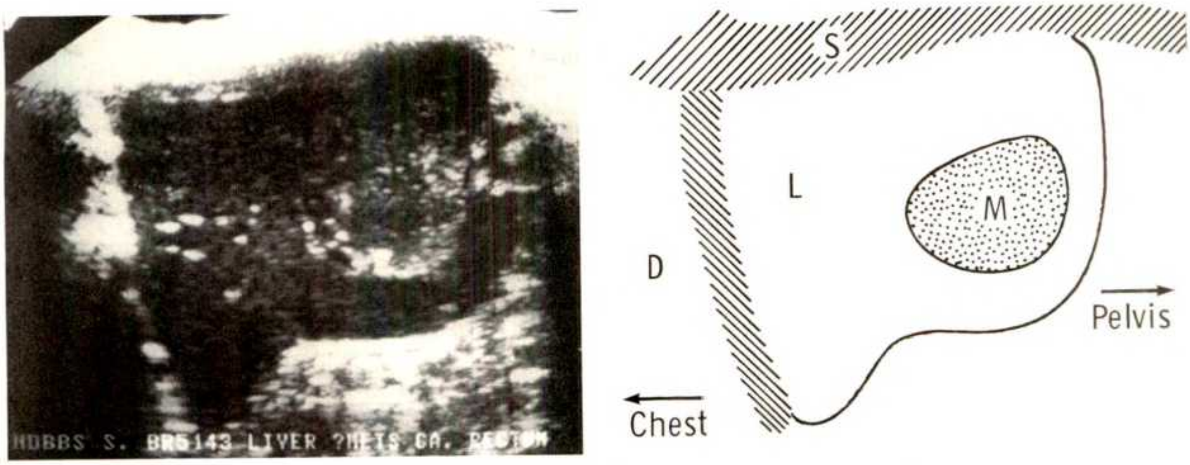


Fig. 1.

A parasagittal scan 6 cm right of mid-line showing skin (S) diaphragm (D) and a highly reflective metastasis (M) in the liver (L).

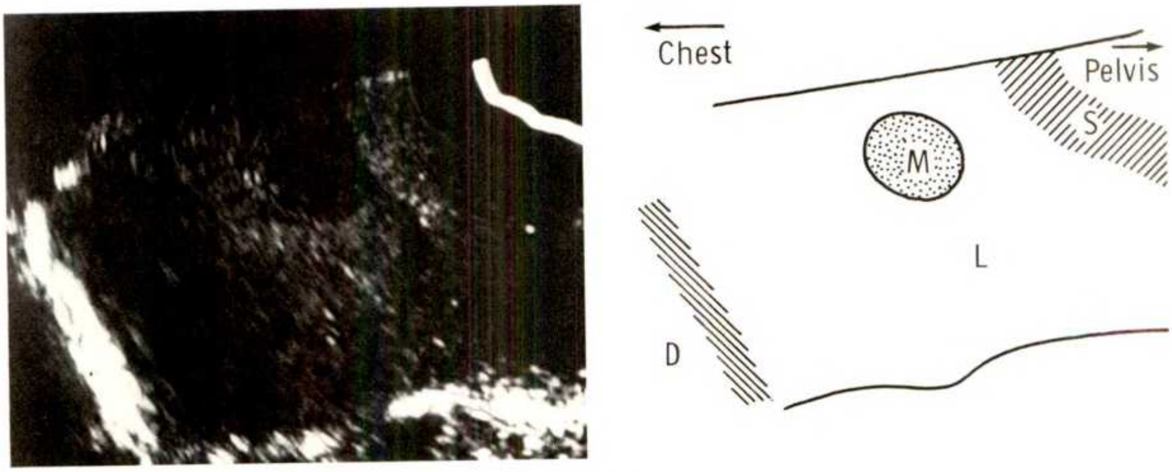


Fig. 2.

Showing a relatively transonic metastases (M) in the liver (L). Skin (S) and diaphragm (D) can also be seen in this parasagittal section.

laparotomy or by Menghini needle) or had clinical hepatomegaly with a high alkaline phosphatase. Many of these patients also had abnormalities of the radioisotope ^{99}Tc scan suggestive of metastases (Table II).

A patient was considered not to have evidence of metastases if no tumour was seen at laparotomy or six months after ultrasound there was no clinical hepatomegaly and a normal alkaline phosphatase. If a ^{99}Tc^{m} scan was performed, it was normal in these patients (Table III).

Of the patients scanned 31 had tumours clinically present and 22 had no signs of tumour at laparotomy, or no signs of tumour six months after ultrasound scanning.

Table IV shows the range of tumours scanned. In four patients (included under "others" in Table IV) a primary could not be identified.

DISCUSSION

The majority of tumours were seen ultrasonically as areas of increased reflectivity within the liver substance (Fig. 1) although some less reflective lesions were also seen (Fig. 2). Many authors believe that liver tumours are generally seen as less reflective areas (Fig. 2) (Melki, 1973). The high proportion of increased reflectivity tumours in our series may be caused by a preponderance of tumours whose primaries lie in the gastrointestinal tract. It is believed by some that metastases for these primaries give more echogenic metastases than normal liver tissue (Taylor, 1974).

It is apparent from the results that ultrasound in the detection of liver tumours has an accuracy of 90% when a satisfactory scan can be obtained (unsatisfactory scans being obtained in 10% of patients).

This study has shown that grey-scale ultrasound has a place to play in the detection of hepatic metastases. Radioisotope scanning has the advantage of being of comparative technical simplicity whereas learning the principles and practice of ultrasound and understanding the ultrasonic appearances of liver tumours can require much training and experience. For the patient, however, ultrasound has the advantage of complete non-invasiveness and safety. It seems probable that, since neither technique gives complete accuracy, both ultrasound and radioisotope scanning should be used side by side in the assessment of hepatic metastases. Ultrasound scanning for liver tumours seems likely to replace radioisotope scanning only in centres which have considerable experience in abdominal ultrasound.

REFERENCES

CONN, H. O., and ELKINGTON, S. G., 1968. Is hepatic scanning over-rated? *Gastroenterology, 54,* 135–139.

DAVIES, R. J., VERNON, M., and CROFT, D. N., 1974. Liver snaps and the detection of clinically unsuspected liver metastases. *Lancet, 1,* 279–280

ETIENNE, J. P., CHAPUT, J. C., and CHOUSTERMAN, M., 1976. Laparoscopy in liver disease. *Lancet, 1,* 1191.

FREEMAN, L. M., BERSTEIN, R. G., and KATZ, M. C., 1969. Coeliac axis angiography in the diagnosis of hepatic secondaries. *Journal of Nuclear Medicine, 10,* 628–631.

JHINGRAM, S. G., JORDAN, L., JAHNS, M. F., and HAYNIE, T. P., 1971. Liver scintigram compared with alkaline phosphatase and BSP determination in the detection of metastatic carcinoma. *Journal of Nuclear Medicine, 12,* 227–230.

MAGNUM, J. F., and POWELL, M. R., 1973. Liver scintiphotography as an index of liver abnormality. *Journal of Nuclear Medicine, 14,* 484–486.

MELKI, G., 1973. Ultrasonic patterns of tumours of the liver. *Journal of Clincical Ultrasound, 1,* 306–314.

SMITH, I. E., TAYLOR, K. J., MCCREADY, V. R., POWLES, T. J., and BONDY, P. K., 1976. A comparison of grey-scale ultrasound with other methods for the detection of liver metastases from breast carcinoma. *Clinical Oncology, 2,* 47–53.

TAYLOR, K. J. W., 1974. Ultrasonic patterns of tumours of the liver. *Journal of Clinical Ultrasound, 1,* 284–287.

TAYLOR, K. J. W., CARPENTER, D. P., and MCCREADY, V. R., 1974. Comparison of ultrasound and radioisotope examination in the diagnosis of hepatobiliary disease. *Journal of Clinical Ultrasound, 2,* 105–116.

Book review

Atlas of Grey Scale Ultrasonography. By K. J. W. Taylor, pp. 411, illus., 1978 (Edinburgh, Churchill Livingstone), £19·50.

This atlas contains a wide range of illustrated case reports covering both abdominal and obstetric scanning and with a few examples from other sites such as the thyroid.

The quality of the scans is, in general, excellent though several of the reproductions are unfortunately too dark.

Since the book is solely an atlas there is no index and minimal discussion of differential diagnosis or the advantages and disadvantages of ultrasound. Dr. Taylor is a well known enthusiast and I found his discussion of the relationship between ultrasound and other techniques a little biased, but nonetheless valuable. Unfortunately, most workers do not obtain results as good as those included here and must not expect to achieve Dr. Taylor's high degree of diagnostic accuracy.

There are very few errors of any sort in this book and the generally high quality of text and figures makes this the best book yet published on the subject of ultrasound. Everyone using diagnostic ultrasound should have access to a copy.

H. B. MEIRE.

1978, *British Journal of Radiology*, *51*, 599–607

AUGUST 1978

An evaluation of the use of ^{99}Tc^{m}-dimercaptosuccinic acid (DMSA) as a static renal imaging agent

By J. B. Bingham, M.A., M.R.C.P.* and M. N. Maisey, M.D., F.R.C.P.

Department of Nuclear Medicine, Guy's Hospital, London Bridge, London SE1 9RT

(*Received October, 1977 and in revised form December, 1977*)

ABSTRACT

The clinical value of ^{99}Tc^{m}-dimercaptosuccinic acid, utilized as a static renal imaging agent, has been analysed in 366 patients. It proved to be diagnostically most useful in space occupying lesions of the kidney when equivocal on IVU and provided useful additional information when used in the determination of divided renal function or the distribution of intrarenal function. Its use is contraindicated in the determination of divided renal function in obstructed kidneys because of accumulation of significant amounts of DMSA that are excreted by glomerular filtration. When DMSA uptake at three hours after injection is compared with ^{99}Tc^{m}-DTPA uptake from 90 to 150 seconds after bolus injection, there is a good correlation between the two methods of determination of divided renal function.

The primary investigation of renal morphology and function is generally accepted as being the intravenous urogram, but it is neither a quantitative, nor an accurate assessment of divided renal function (Hoffman and Grayhack, 1960; Wilkiemeyer *et al.*, 1972). Consequently, additional methods are needed when more exact determination of function is required. Bilateral ureteric catheterization with urinary sampling is relatively invasive, as is the renal angiography required for densitometric renal function determination (Bolin, 1960).

Renal investigation with radiopharmaceuticals provides a reliable, atraumatic method for comparing individual renal function quantitatively. Radioactive tracers used for renal study are divided into two basic groups, firstly, those that are excreted by glomerular filtration, such as the metal complexes with E.D.T.A. and, secondly, those that are fixed in the renal parenchyma, such as the organic mercurials, although there is considerable overlap. The latter group is ideal for use as static renal imaging agents as the tracer remains sufficiently long in the renal cortex to allow good resolution images to be obtained.

The first static imaging agent utilized was Neohydrin labelled with ^{203}Hg (McAfee and Wagner, 1960) but because of the relatively long half-life of 47 days and consequent high radiation dose, it was replaced by ^{197}Hg labelled organomercurials, reducing the radiation dose considerably. Unfortunately, the gamma emission of ^{197}Hg (77 Kev) is less than ideal for imaging with a gamma camera and the poor tissue penetration of the gamma rays is another serious disadvantage.

^{99}Tc^{m} has ideal imaging characteristics for use with the gamma camera and has a sufficiently short half-life to minimize patient radiation dose. A number of radiopharmaceuticals have been developed using this isotope for renal imaging, such as ^{99}Tc^{m}—gluconate (Charamza and Budikova, 1969), ^{99}Tc^{m}—glucoheptonate and ^{99}Tc^{m}—caseidin (Winchell *et al.*, 1971). When technetium is chelated by 2,3 dimercaptosuccinic acid, which is avidly taken up by renal parenchyma, a very satisfactory static renal imaging agent is obtained (Lin *et al.*, 1974; Enlander *et al.*, 1974; Handmaker *et al.*, 1975).

When the preparation is injected intravenously, approximately 50% of the administered dose is localized in the kidneys by one hour and there is an exceptionally high cortex to medulla ratio, with excretion into the urine usually insufficient to cause pelvic artifacts. High doses of DMSA (1–2 G) were used during an anti-schistosomiasis campaign in the People's Republic of China and no significant toxicity was reported (Wang *et al.*, 1965). Clinical use as an imaging agent requires less than 1 mg of DMSA, thus implying a large safety margin.

The purpose of this study is to determine the indications for referral for static renal imaging and to assess, semiquantitatively, the contribution to diagnostic probability of imaging with this radiopharmaceutical in relation to other diagnostic procedures.

MATERIALS AND METHOD

Imaging techniques

^{99}Tc^{m} labelled dimercaptosuccinic acid is prepared in our laboratory by the method of Lin *et al.*, (1974) and approximately 220 MBq (6 mCi) are injected intravenously within thirty minutes of preparation. Lower doses of radioactivity are administered to children in proportion to their surface area. Imaging is then carried out at three hours after injection using Ohio Nuclear series 100 or 110 gamma cameras with high resolution collimators collecting 300000 counts on 70 mm, Polaroid or 10×8 in nuclear medicine film (Kodak). Simultaneously, data are required in a PDP 11 dedicated minicomputer for later, off-line analysis. Quantitation of the uptake of DMSA into each kidney is determined using the irregular region of interest facility of the computer and the ratio of counts in each kidney, after background subtraction, calculated. Routinely, an area of background inferior and lateral to the right kidney is used (Fig. 1). Overall renal function is usually estimated separately and we usually use ^{51}Cr-EDTA for this purpose, as a measure of the glomerular filtration rate (Garnett *et al.*, 1967; Chantler, *et al.*, 1969).

---

*Present address: Department of Nuclear Medicine, Massachusetts General Hospital, Boston, Mass. 02114, USA. All correspondence to M. N. Maisey.

A comparison of divided function as determined by DMSA was made with that using ^{99}Tc^{m} labelled diethylenetriaminepentaacetic acid (DTPA) (Diagnostic Isotopes Inc.) in 38 patients on whom both radiopharmaceuticals had been used within a short period. No special preparations were carried out.

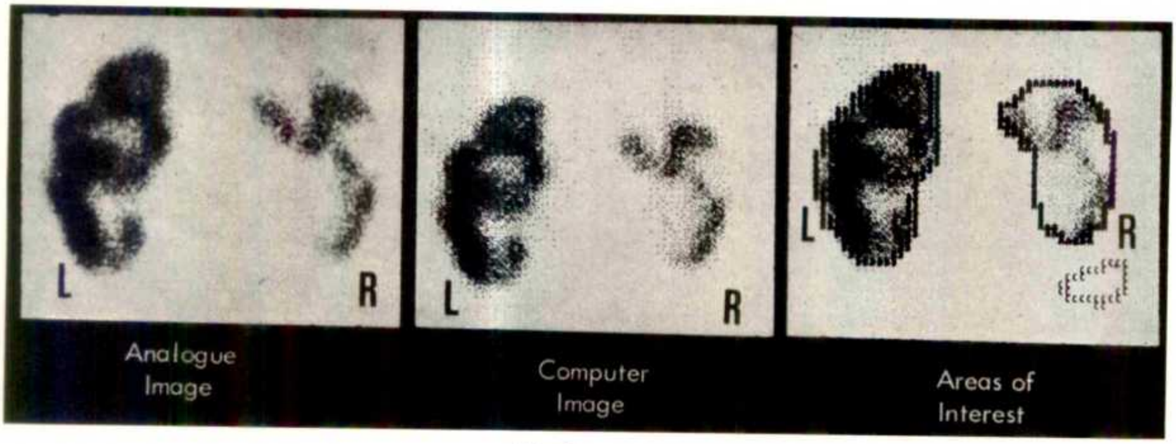


FIG. 1.

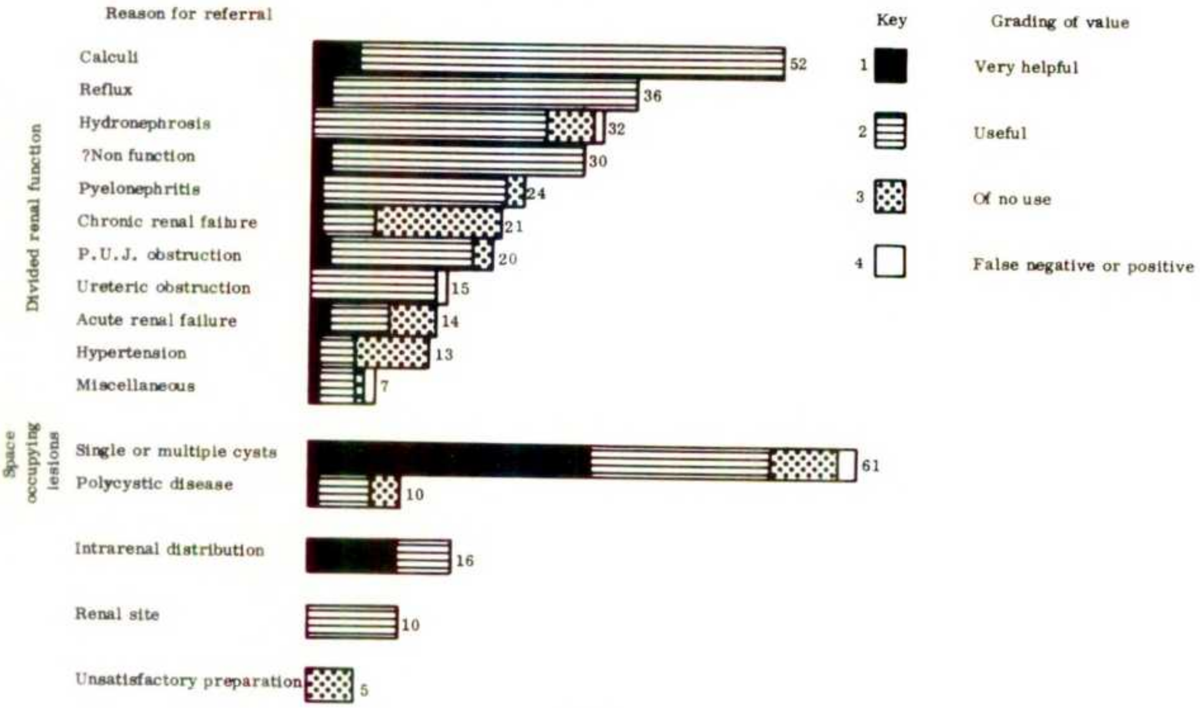


FIG. 2.

The reasons for referral vs. the value of a static ^{99}Tc^{m} DMSA renal study in 366 patients.

The divided function using DTPA was obtained by determining the uptake into each kidney from 90 to 150 seconds following a bolus injection of approximately 550 MBq (15 mCi) of the radiopharmaceutical as suggested by Britton (1975), again utilizing the area of interest facility of the computer and a similar background area to that used for DMSA.

Clinical studies

Three hundred and sixty-six studies with DMSA performed in the last three years on patients referred for renal imaging have been retrospectively broken down into diagnostic groups and have then been further graded in order of diagnostic usefulness.

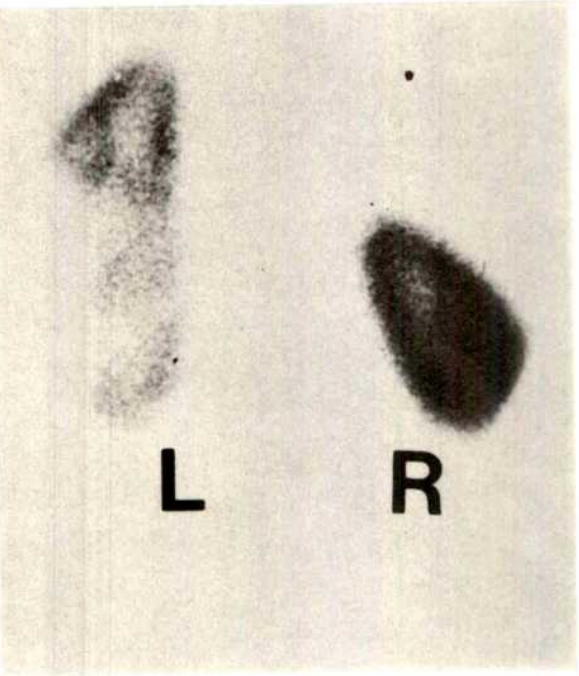
Grading system

Grade 1: The diagnosis was altered or information gained that was not readily available by other means.

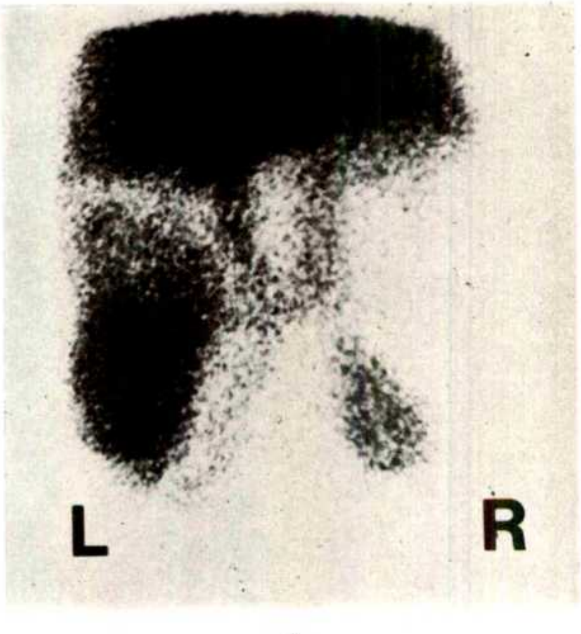
Grade 2: Additional or confirmatory information was obtained but no change in diagnosis was achieved.

Grade 3: No contribution to previous information or diagnosis was gained.

Grade 4: The information gained was incorrect as shown by subsequent investigation.



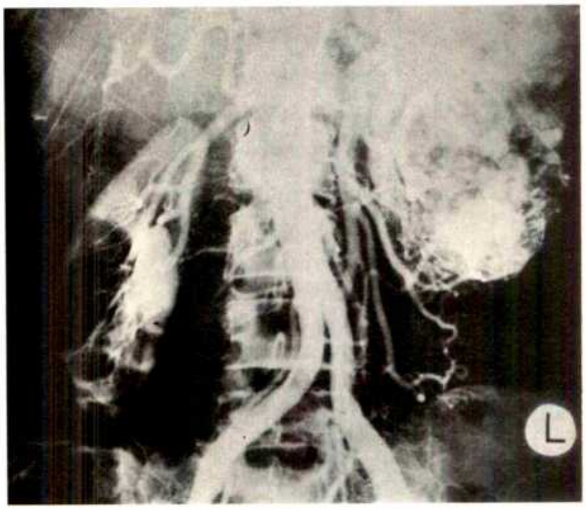
B



A

FIG. 3.

(A) Integrated image of the first 30 seconds following the bolus injection of DMSA.



C

FIG. 3.

(B) 3 hour image.

(C) Renal arteriogram.

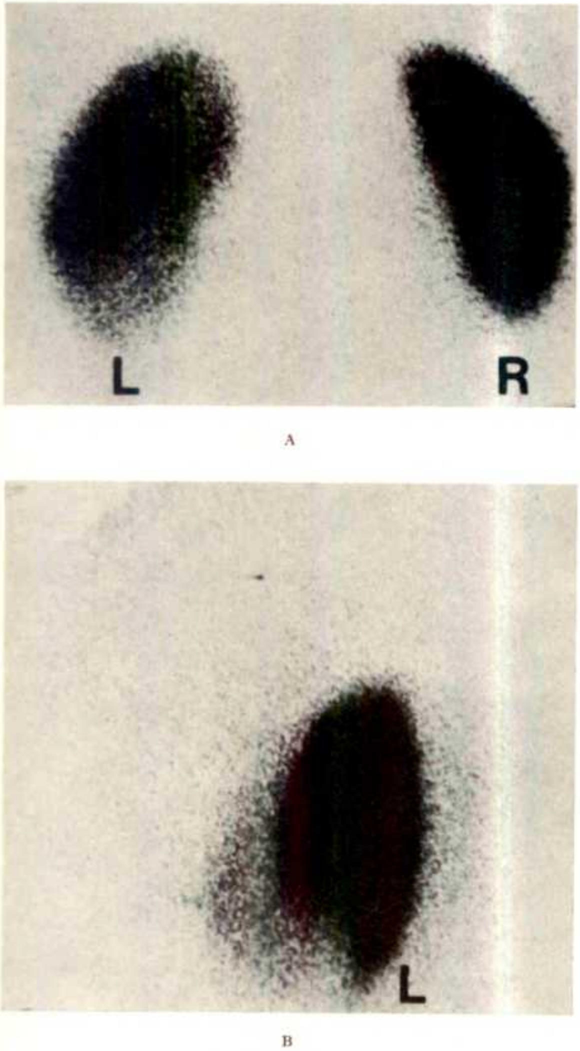


FIG. 4.

(A) Posterior view
(B) Lateral view of the left kidney: Space occupying lesion at the lower pole.

RESULTS

The analysis of the 366 patient studies is shown in Fig. 2. The histogram shows that the use of DMSA proved to be of most diagnostic value in those patients who had space occupying lesions of the kidney. It was of no value when the lesions were clearly seen on the IVU but had a high diagnostic value when lesions were equivocal. We found it essential to take the studies in conjunction with the IVU and to remember that lesions of less than about 2.5 cm in diameter were unlikely to be resolved (Morales, 1974). Similarly, small lesions in the pelvis were liable to be missed due to the absence of

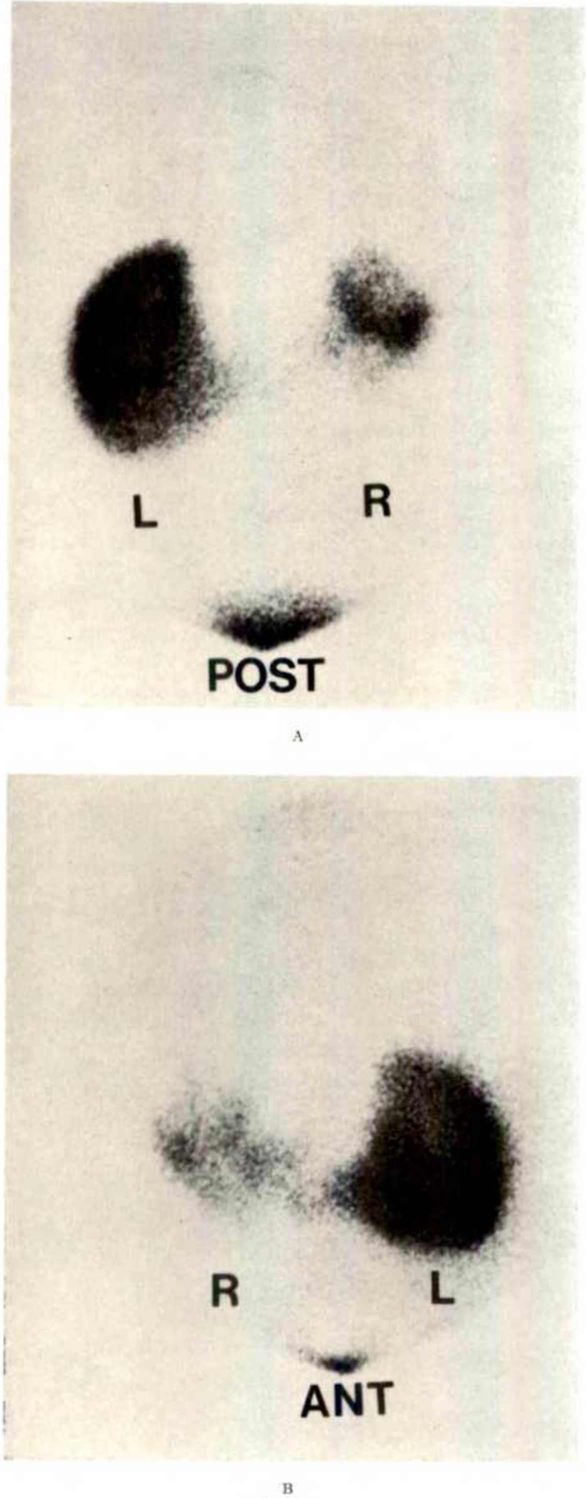


FIG. 5.
Horseshoe kidney.
(A) Posterior
(B) Anterior

surrounding functioning renal tissue. The site of calyces and pelvis seen on IVU should always be compared to the renal image.

Dynamic imaging following the bolus injection of 370 MBq (10 mCi) of DMSA intravenously may be of value for showing the vascularity of lesions as illustrated by Fig. 3 where Fig. 3A shows the integrated image over the first 30 seconds after injection, with a highly vascular lesion in the lower pole of the left kidney, which in Fig. 3B shows absent uptake of DMSA at three hours after injection. The renal arteriogram Fig. 3C performed later demonstrated the hypervascular hypernephroma of the lower pole of the left kidney. Alternatively, having established the best position in which to image the space occupying lesion using the DMSA image, autologous $^{99}Tc^{m}$ labelled red cells may be used to assess vascularity. Fig. 4 shows how important extra views may be in further delineating a lesion. A metastatic deposit was just visible in the routine posterior view (Fig. 4A) at the lower pole of the left kidney but was much more clearly defined in the left lateral projection (Fig. 4B).

Most of the negative DMSA studies were not further investigated, but three in whom the study was negative had arteriography performed because the clinical suspicion was sufficient to warrant it and all three had negative arteriograms. One negative study had a further IVU with high dose nephrotomography which showed up probable, small, multiple cysts. Two further negatives had retrograde catheterizations performed, one of which was also negative, the other showed a small para-pelvic cyst and on review of the DMSA study this was just visible. One study showed a space occupying lesion which then proved to be arteriographically negative but neither DMSA study nor the arteriogram is available for review.

DMSA is one of the primary investigations in iodine sensitive patients as illustrated by the study of a man who was in atrial fibrillation and suddenly developed right loin pain. His study showed a wedge-shaped cortical defect on the right, which was thought to be a renal infarct.

Polycystic kidneys show multiple defects of DMSA accumulation but usually the diagnosis was obvious from the IVU alone.

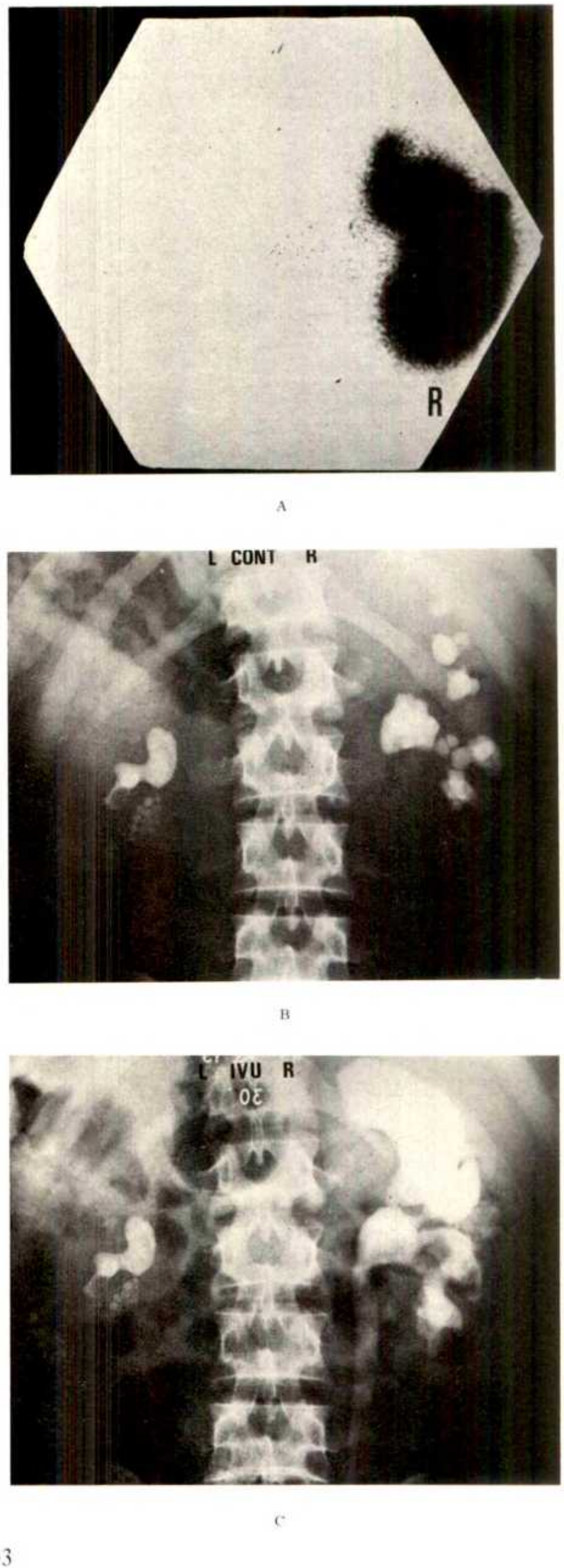


FIG. 6.
(A) Posterior DMSA study.
(B) Control X-ray.
(C) IVU.

Determination of intrarenal distribution of function frequently proved of value. Fig. 5A shows a horseshoe kidney with good delineation of the interrenal bridge. In this instance, the anterior view (Fig. 5B) shows the bridge better and we now perform

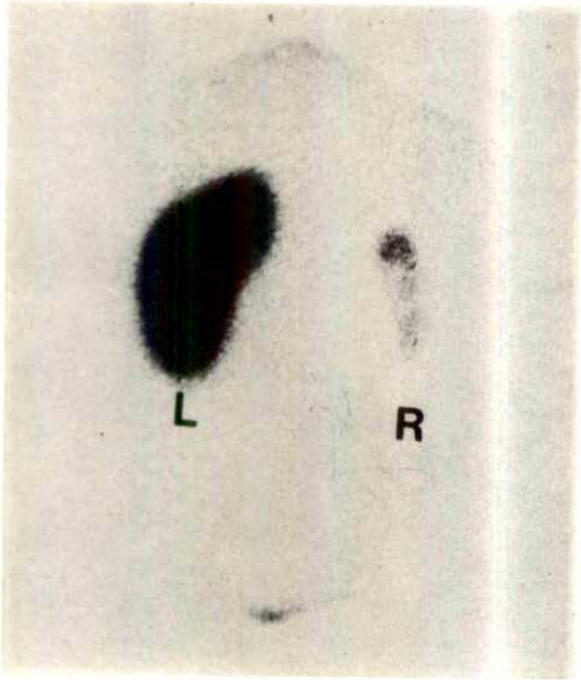


FIG. 7.
Pyelonephritic right kidney.

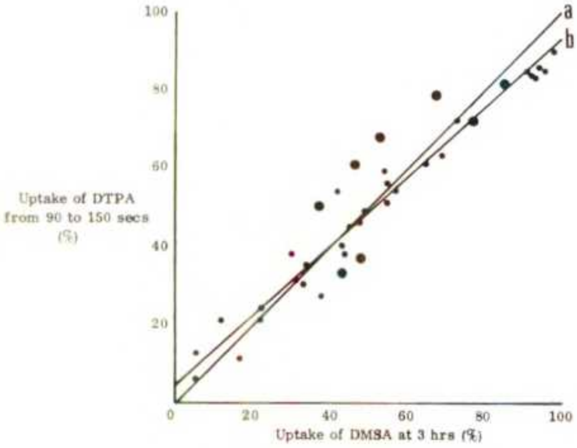
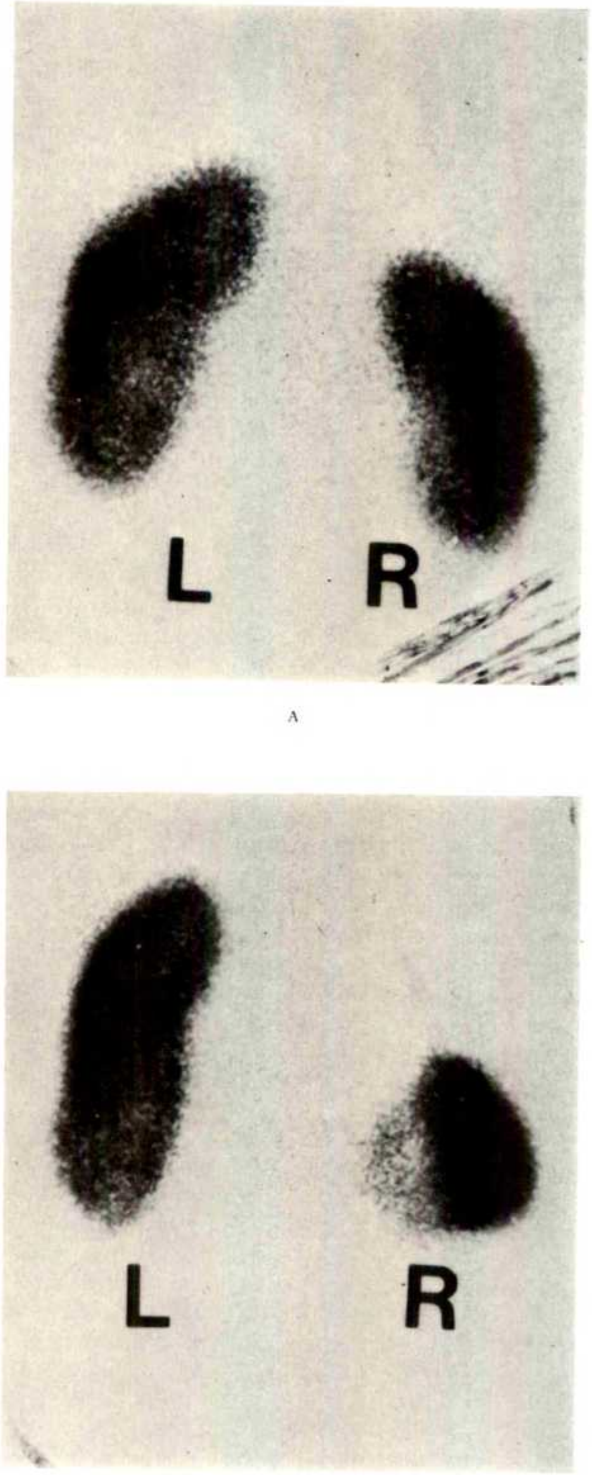


FIG. 8.
Determination of the function of the right kidney as a percentage of the overall function in 38 patients using DMSA and DTPA. The larger points are studies where one kidney was obstructed.
(a) = line of exact agreement. (b) = line of best fit. ($r = 0.959$, $p < 0.001$)



A

B

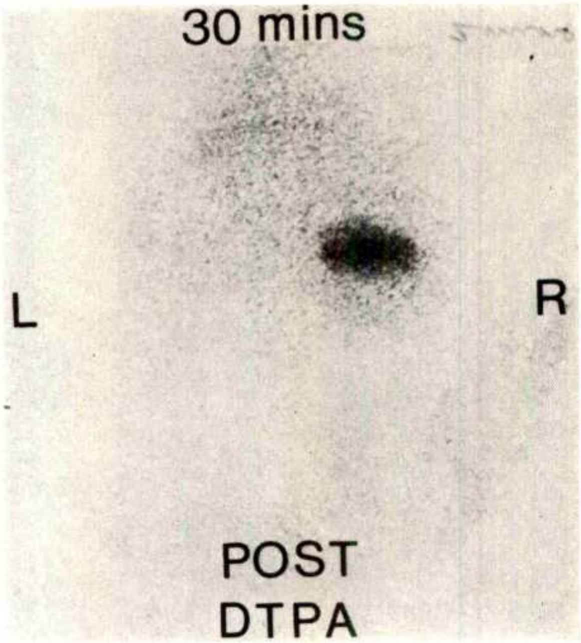
FIG. 9.
Nephroptosis (A) Lying.
(B) Sitting.

both anterior and posterior views in patients suspected of having horseshoe kidneys.

Figure 6A shows the DMSA study in a patient with bilateral calculi and an essentially non-functioning left kidney. The functioning parenchyma was demonstrated well, allowing the surgeon to plan his approach. Fig. 6B shows the control film and 6C the IVU of the same patient. (Both X-rays are reversed for comparison with the DMSA study.)

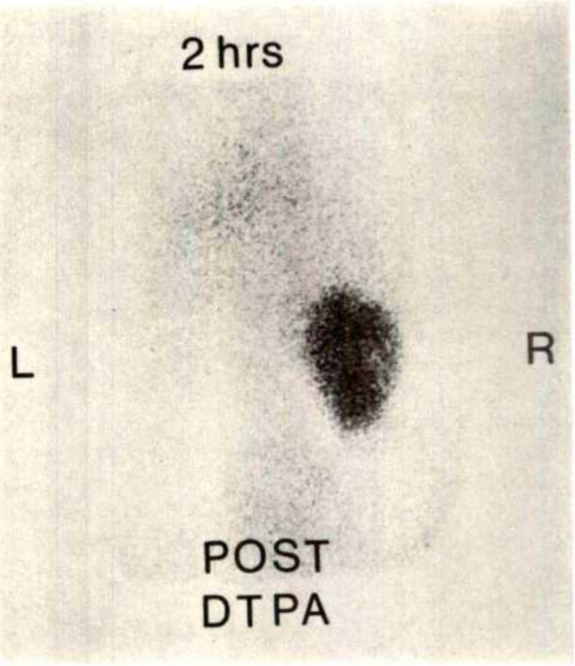
Kidney positions are readily marked on the skin in the prone position prior to biopsy and kidneys can be easily sited in relation to other nuclear medicine procedures, such as adrenal scanning.

It was gradually appreciated that the use of DMSA as an agent for demonstrating anatomical defects of renal parenchyma was likely to diminish with the introduction of ultrasound, high dose nephrotomography and computed tomography because of the better inherent resolution of these techniques, so that DMSA was increasingly used for the determination of divided function and in these instances, though supplying important functional information for preoperative assessment of renal function, it was rarely of diagnostic value. Figure 7 illustrates the use of DMSA in a man with pyelonephritis of the right kidney where the question was "how much function there remained in the damaged kidney?" At the same time, the scarring

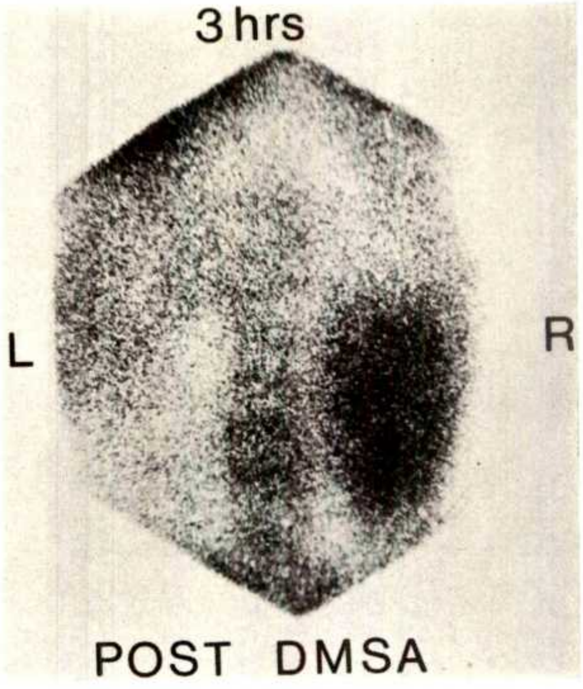


A

FIG. 10.



B



C

FIG. 10.

(A), (B), DTPA study of a solitary, obstructed right kidney. (C) DMSA study of the same patient.

from pyelonephritis may be noted and may be used to delineate early parenchymal damage (Merrick, 1977).

Figure 8 shows the comparison of the three hour uptake of DMSA with that of DTPA as an assessment of the function of the right kidney of 38 patients. There is good correlation between the two methods, the regression coefficient being 0.959 ($p < 0.001$). The larger points represent patients who had one obstructed kidney (not necessarily the right).

The main problems associated with determination of divided function by this method were, firstly, nephroptosis, particularly when unilateral, as this may alter considerably the activity measured in the ptosed kidney. This is illustrated in Fig. 9A where the kidneys are seen in the lying position and in Fig. 9B where the right kidney has flopped forward. All our patients are now imaged supine with knees flexed to reduce the lumbar lordosis. Secondly, in severely obstructed kidneys, the small quantity of DMSA that is excreted by glomerular filtration is sufficient to cause a large increase in counts from the obstructed pelvis. This is shown in Fig. 10, showing scans in a patient with a solitary right kidney and very poor renal function. At 30 minutes after injection of DTPA (Fig. 10A), a rim of functioning tissue is visible at the upper pole of the kidney and by two hours after injection (Fig. 10B) the whole pelvis has filled. On the DMSA study at three hours after injection (Fig. 10C) the retention of filtered DMSA in the pelvis of the kidney is sufficient to obscure the functioning parenchyma in the upper pole.

In five patients, the preparation of the radiopharmaceutical was unsatisfactory and this was characterized by excessive uptake in liver and spleen.

DISCUSSION

DMSA as an agent for demonstrating defects of the renal parenchyma has proved very useful, though likely to be displaced by ultrasound. However, it may remain of use for those patients with hypertrophy of the septa of Bertin or "pseudotumours" of the kidney and fetal lobulation which will show up as solid lesions on ultrasound but will exhibit normal, or possibly increased DMSA accumulation (Caplan *et al.*, 1968; Braunstein *et al.*, 1972; Parker *et al.*, 1976). It is of value for assessing divided function and its close correlation with DTPA uptake, DTPA being a radiopharmaceutical which is entirely handled by the kidney as glomerular filtrate (Klopper *et al.*, 1972; Hilson *et al.*, 1976), supports the concept of a single uptake function for the kidney with the traditional measurements, GFR with inulin and renal plasma flow with the clearance of PAH being interdependant rather than independant (Britton and Brown, 1971). With marked degrees of unilateral renal impairment on one side, the relative function of the affected side determined with DTPA tends to be higher than that with DMSA. This is likely to be related to the difficulties experienced with finding a suitable background area for DTPA. With DMSA the target to non-target ratio is much greater than with DTPA so that the background area chosen is much less critical. However, with declining total renal function, uptake in the kidneys is reduced and uptake in the liver and spleen relatively increased so that the estimate of divided renal function in chronic renal failure is liable to be very much more inaccurate.

As a measure of divided function, DMSA is unsuitable for the severely obstructed kidney because of the hold-up of filtered DMSA in the dilated pelvis. In Fig. 8 where the studies with obstructed kidneys are indicated by larger points, there is marked deviation from the line of exact identity between the two methods. In these circumstances, DTPA is probably more appropriate for the determination of divided function.

Measurement of the overall renal function with DMSA in a similar method to that used with ^{197}Hg chlormerodrin (Raynaud *et al.*, 1968) is unlikely to be as successful in view of the multiple ^{99}Tc^{m}—DMSA complexes of variable renal affinity formed with changing concentrations of pertechnetate and tin (Ikeda *et al.*, 1976).

DOSIMETRY

In view of the high and rapid renal concentration of DMSA, the kidneys are the critical organ for radiation dose estimates. The dosimetry for DMSA, DTPA and chlormerodrin is shown in Table I (Arnold *et al.*, 1975; Hauser *et al.*, 1970; McAfee, 1970).

TABLE I

RADIATION DOSIMETRY OF DMSA, DTPA and ^{197}HG CHLORMERODRIN

	μGy/MBq		
Organ	DMSA	DTPA	^{197}Hg Chlor.
Kidneys	168	11.4	3351
Bladder	76	150	
Whole Body	4.3	4.3	

In situations where there is significant renal impairment, the renal radiation dose will be reduced and the whole body dose increased.

CONCLUSION

DMSA has proved to be of diagnostic value for the delineation of space occupying lesions of the kidney, to give useful additional information when assessing divided renal function and determining intrarenal distribution of function but to add little useful diagnostic information in chronic renal failure. Divided function determined with DMSA correlates well with that using DTPA.

REFERENCES

Arnold, R. W., Subramanian, G., McAfee, J. G., Blair, R. J., and Deaver, Thomas, F., 1975. Comparison of ^{99}Tc^{m} complexes for renal imaging. *Journal of Nuclear Medicine, 16,* 357–367.

Bolin, H., 1960. Contrast medium in the kidney during angiography—A densitometric method for estimation of renal function. *Acta Radiologica Scandinavia* (*Stockholm*), *Supplement 257.*

Braunstein, P., Hernberg, J. G., Bosniak, M. A., and Barasch, E., 1972. Scintiscan evaluation of prominent renal columns. *Radiology, 104,* 103–106.

Britton, K. E., 1975. Renal function studies with radioisotopes. In *Dynamic studies with radioisotopes in clinical medicine and research, 1974,* Vol I, 215–217. (IAEA, Vienna).

Britton, K. E., and Brown, N. J., 1971. *Clinical Renography.* Lloyd-Luke.

Caplan, G. E., Hartmann, H. R., Young, R., and Victor, I., 1968. The "hot" renal tumour. Scanning and angiographic characteristics of a solid renal tubular adenoma. *Radiology, 91,* 991–992.

Chantler, C., Garnett, E. S., Parsons, V., and Veall, N., 1969. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr-EDTA. *Clinical Science, 37,* 169–180.

Charamza, O., and Budikova, M., 1969. Method of preparation of a ^{99}Tc^{m} tin complex for renalscintigraphy. *Nuclear Medicine* (*Stuttgart*), *8,* 301–305.

Enlander, D., Weber, P. M., and dos Remedios, L. V., 1974. Renal cortical imaging in 35 patients: superior quality with ^{99}Tc^{m} DMSA. *Journal of Nuclear Medicine, 15,* 743–749.

Garnett, E. S., Parsons, V., and Veall, N., 1967. Measurement of glomerular filtration rate in man using a ^{51}Cr edetic acid complex. *Lancet I,* 818–819.

Handmaker, H., Young, B. W., and Lowenstein, J. M., 1975. Clinical experience with ^{99}Tc^{m} DMSA (dimercaptosuccinic acid) a new renal imaging agent. *Journal of Nuclear Medicine, 16,* 28–32.

Hauser, W., Atkins, H. L., Nelson, K. G., and Richards, P., 1970. Technetium 99m-DTPA: a new radiopharmaceutical for brain and kidney scanning. *Radiology, 94,* 679–684.

Hilson, A. J. W., Mistry, R. D., and Maisey, M. N., 1976. ^{99}Tc^{m}-DTPA for the measurement of glomerular filtration rate. *British Journal of Radiology, 49,* 794–796.

Hoffman, W. W., and Grayhack, J. T., 1960. The limitations of the intravenous pyelogram as a test of renal function. *Surgery, Gynaecology and Obstetrics, 110,* 503–509.

Ikeda, I., Inoue, O., and Kurata, K., 1976. Chemical and biological studies on ^{99}Tc^{m}DMS-II: Effect of Sn (II) on the formation of various Tc DMS complexes. *International Journal of Applied Radiation and Isotopes, 27,* 681–688.

Klopper, J. F., Hauser, W., Atkins, H. L., Eckelman, W. C., and Richards, P., 1972. Evaluation of ^{99}Tc^{m}-DTPA for the measurement of glomerular filtration rate. *Journal of Nuclear Medicine, 13,* 107–110.

Lin, T. H., Khentigan, A., and Winchell, H. S., 1974. A ^{99}Tc^{m} chelate substitute for organoradiomercurial renal agents. *Journal of Nuclear Medicine, 15,* 34–35.

McAfee, J. G., 1970. Problems in evaluating the radiation dose for radionuclides excreted by the kidneys. In *Medical Radionuclides: Radiation dose and effects,* Edited by Cloutier, R. J., Edwards, C. L. and Snyder, W. S. Conf. 691212, U.S.A.E.C., 271–294.

McAfee, J. G., and Wagner, H. N., 1960. Visualization of the renal parenchyma by scintiscanning with ^{203}Neohydrin. *Radiology, 75,* 820–821.

Merrick, M. V., 1977. Investigation of urinary infections in children. British Nuclear Medicine Society, Fifth Annual Meeting (unpublished).

Morales, J. O., 1974. Space occupying lesions of the kidney. *Seminars in Nuclear Medicine, 4,* 133–149.

Parker, J. A., Lebowitz, R., Mascatello, V., and Treves, S., 1976. Magnification renal scintigraphy in the differential diagnosis of septa of Bertin. *Paediatric Radiology, 4,* 157–160.

Raynaud, C., Desgrez, A., and Kellershohn, C., 1968. Measurement of renal mercury uptake by external counting: separate functional testing of each kidney *Journal of Urology, 99,* 248–263.

Wang, S. C., Ting, K. S., and Wu C. C., 1965. Chelang therapy with NA-DMS in occupational lead and mercury intoxication. *Chinese Medical Journal, 84,* 437–439.

Wilkiemeyer, R. M., Boyce, W. H., and Malek, R. S., 1972. Validity of the intravenous pyelogram in assessment of renal function. *Surgery, Gynaecology and Obstetrics, 135,* 897–900.

Winchell, H. S., Lin, M. S., and Shipley, B. A., 1971. Localization of polypeptide caseidin in the renal cortex: a new radioisotope carrier for renal studies. *Journal of Nuclear Medicine, 12,* 678–682.

1978, *British Journal of Radiology*, *51*, 608–612

Response of aneurysmal bone cyst to low doses of cobalt 60 gamma radiation with prolonged treatment

By V. Shah, M.D., D.M.R.D., D.M.R.T., N. C. Singhal, M.Sc., Ph.D., and
J. P. Udawat, D.M.R.D. (R.C.P.&S.) Eng.

Department of Radiology, SMS Hospital and College, Jaipur, India

(*Received February, 1977 and in revised form September, 1977*)

ABSTRACT

Successful treatment of two cases of aneurysmal bone cyst by cobalt 60 gamma radiation using low doses over prolonged periods (1400 rad in seven weeks and 1600 rad in eight months) is reported. Follow-up of four to ten years duration does not reveal any recurrence or complications. The merit of low dose, prolonged interval irradiation over surgery is discussed. This technique is recommended for aneurysmal bone cysts in children, especially at inaccessible sites.

Aneurysmal bone cyst is a distinct, highly vascular, bone lesion with classical radiographic and pathological characteristics. Jaffe and Lichtenstein (1942) were the first to use the term aneurysmal bone cyst and they proclaimed it to be a distinct entity.

Our two cases of aneurysmal bone cyst were treated by cobalt 60 teletherapy using a prolonged course of radiation therapy. Both cases were followed up and radiographs were taken regularly to assess the results of radiotherapy.

CASE REPORTS

Case 1

A six-year-old Christian boy presented in August, 1973, with pain and swelling just below the left knee joint and

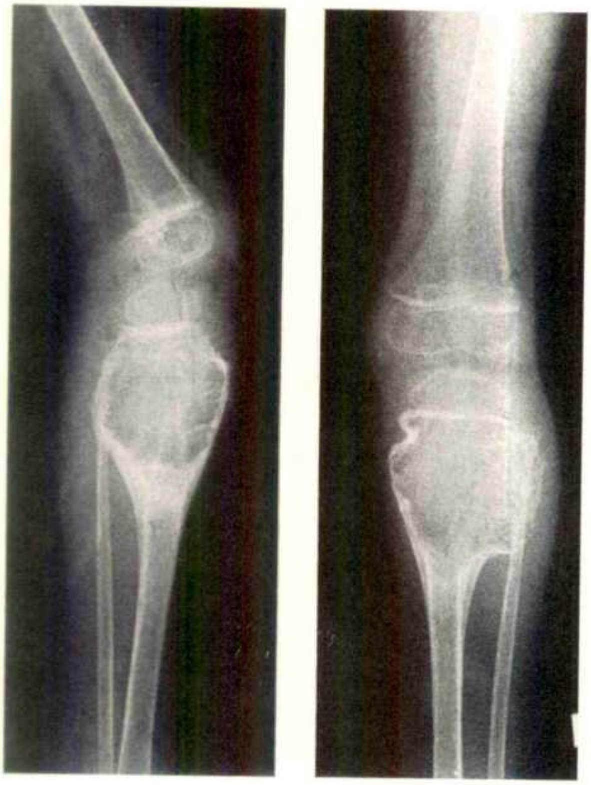


FIG. 1. *Case 1.*

Radiograph (before radiotherapy) reveals a fusiform expanded lesion located eccentrically in relation to the long axis of the shaft of tibia involving the metaphysis and part of the diaphysis. Faint trabeculations are seen through the translucent area giving the soap bubble appearance of an aneurysmal bone cyst.

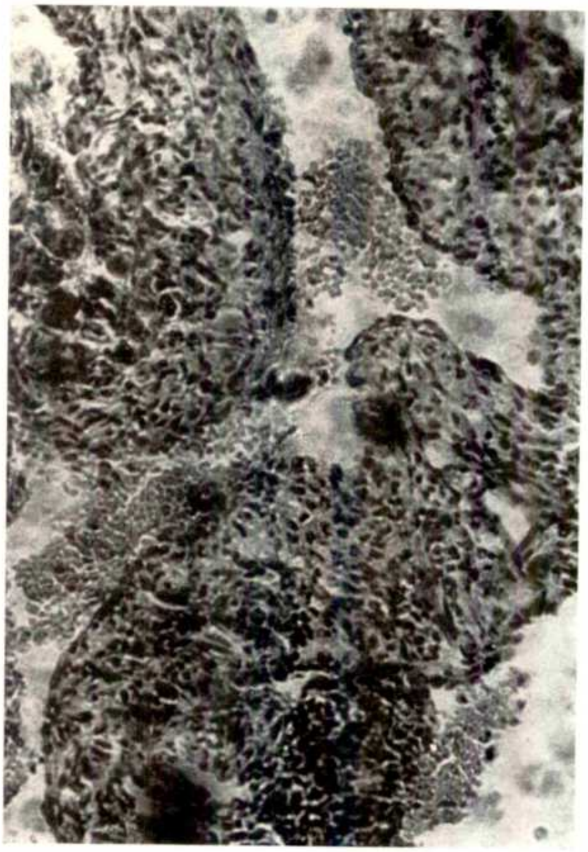


FIG. 2.

Microphotograph of Case 1 showing large spaces and various small slit-like spaces separated by fibrous stroma containing giant cells.

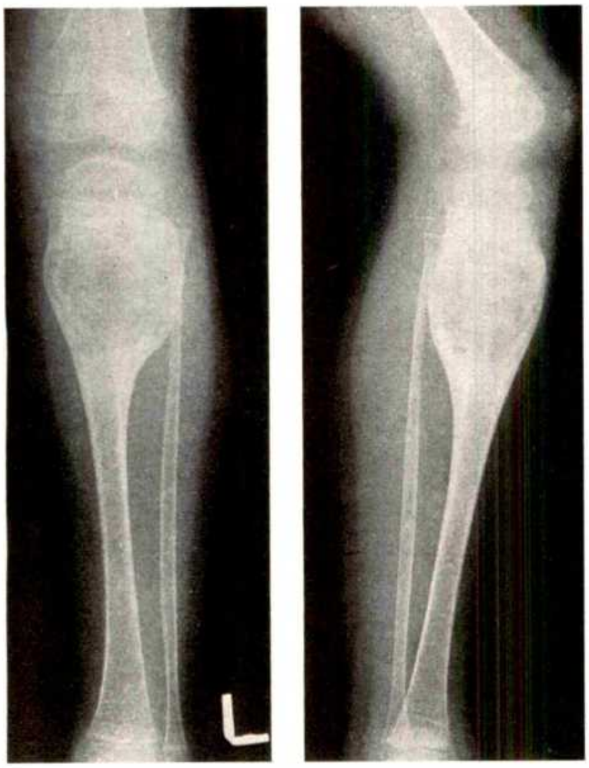


FIG. 3. *Case 1.*

Radiograph taken five months after radiotherapy showing the presence of calcification and reduction in size of the cyst.

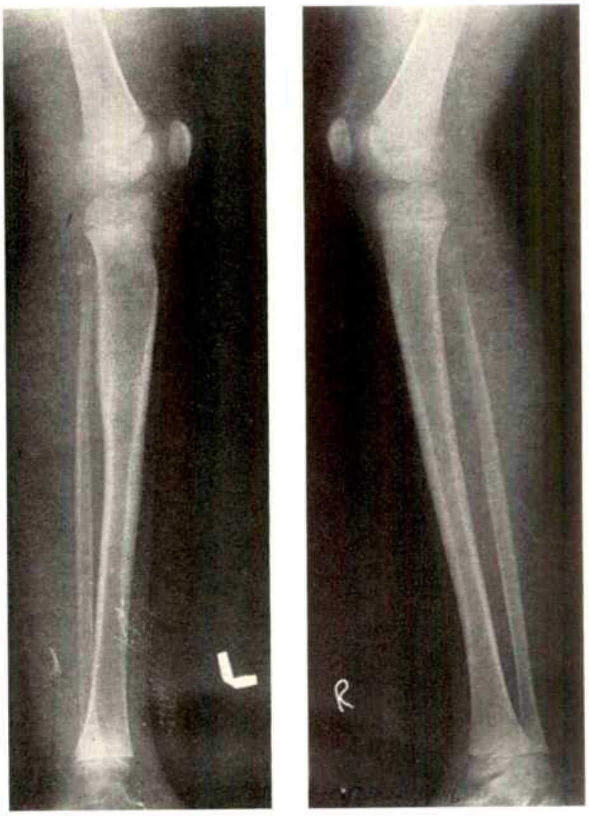


FIG. 4B. *Case 1.*

Radiograph lateral view of both legs taken four years after radiotherapy showing complete healing of the lesion of the left tibia, compared with normal right tibia.

difficulty in walking. Radiography (Fig. 1) revealed a fusiform, expanded lesion located eccentrically in relation to the long axis of the shaft of tibia. The cystic lesion was near the epiphysis, involving the metaphysis and part of the diaphysis. Faint trabeculations were seen through the area of translucency, producing the soap bubble appearance. Exploration revealed an extensive, destructive, highly vascular non-resectable cyst. The histopathological picture (Fig. 2) revealed slit-like vascular spaces, giant cells with stroma varying in cellularity from loose to compact and consisting mainly of spindle shaped cells, and extensive areas of haemorrhage. The lesion was treated by cobalt 60 teletherapy to the upper half of the left leg using parallel opposed 8.5 × 8 cm fields. A mid-line tumour dose of 1400 rad in seven fractions was delivered in seven weeks (one fraction of 200 rad per week). A radiograph taken five

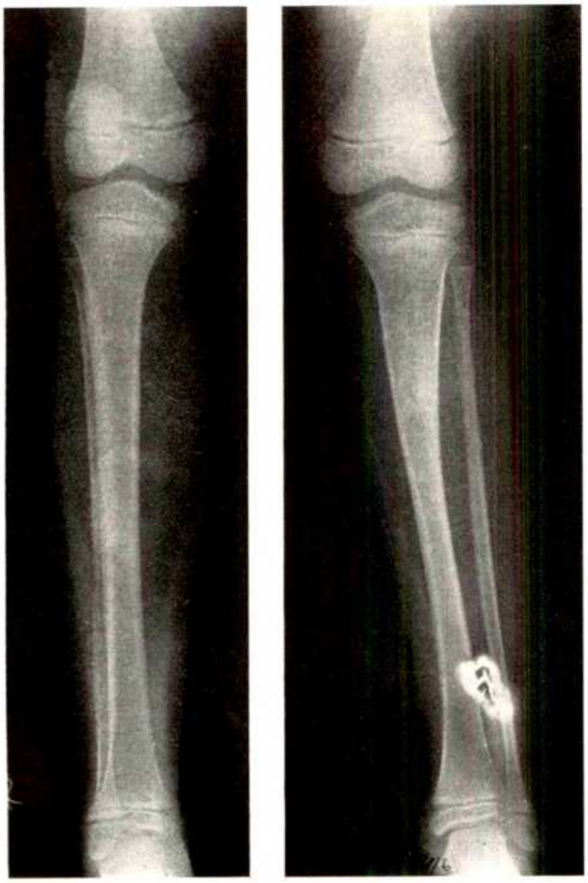


FIG. 4A. *Case 1.*

Radiograph A.P. view of both legs taken four years after radiotherapy showing complete healing of the lesion of the left tibia, compared with the normal right tibia.

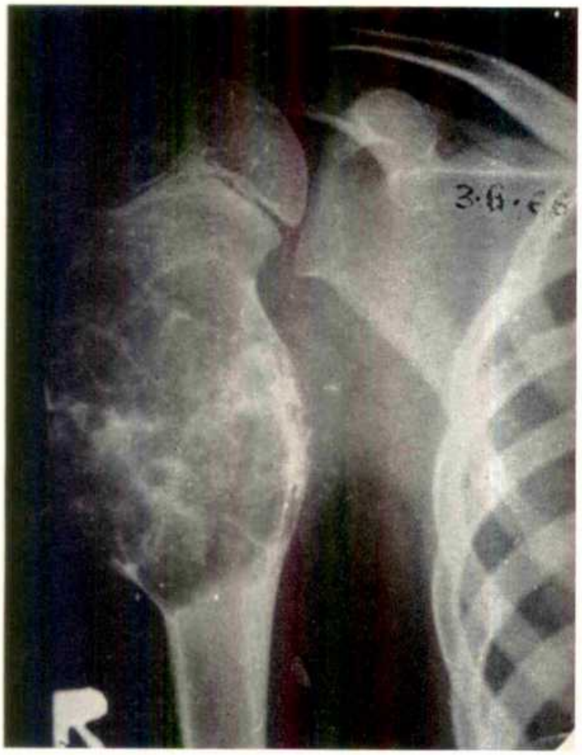


Fig. 5. *Case 2.*

Radiograph (before radiotherapy) reveals destruction of the right upper humerus with a cystic appearance involving the metaphysis and part of the diaphysis with a fusiform expanded lesion, located eccentrically.

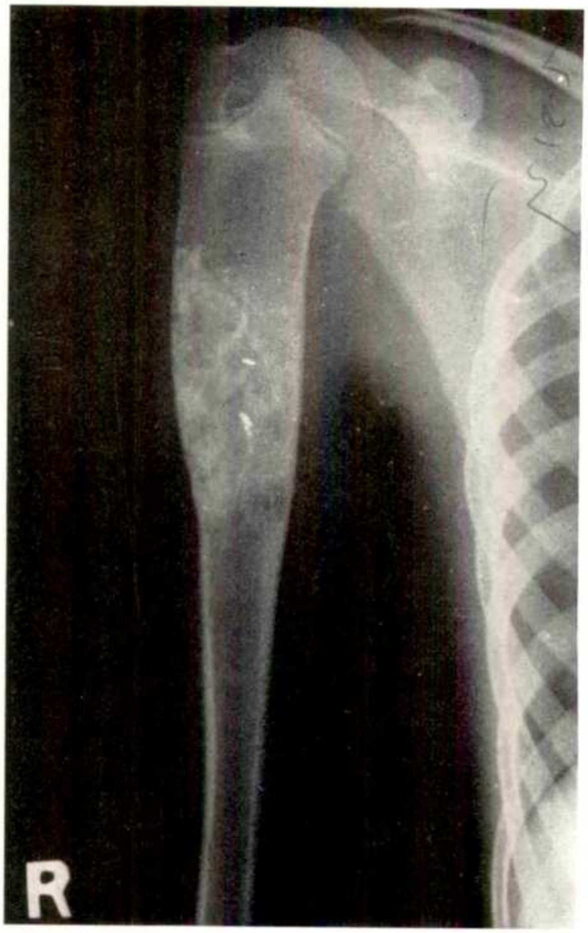


Fig. 7. *Case 2.*

Radiograph taken after completion of radiotherapy showing regression of the lesion with recalcification.

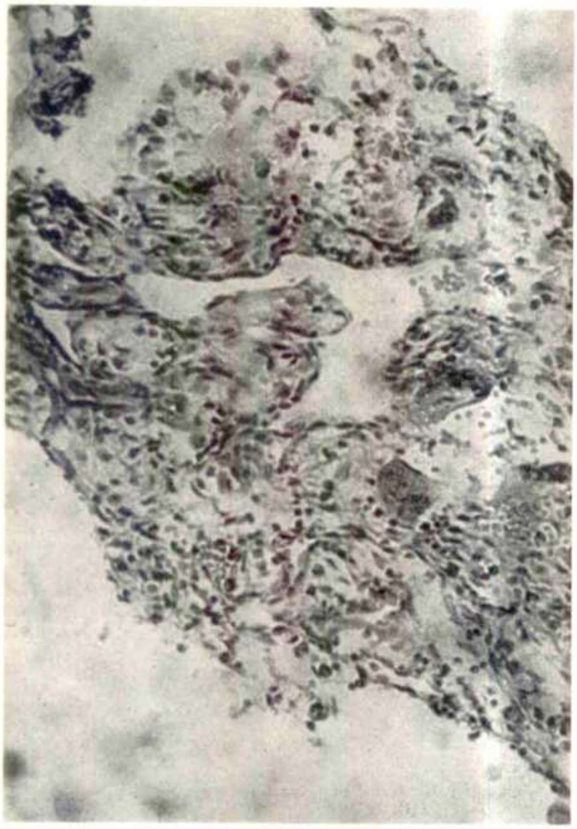


Fig. 6.

Microphotograph of Case 2 showing a few slit-like spaces containing red blood corpuscles. The stroma is loose and contains a few giant cells.

months after therapy (Fig. 3) revealed the gradual reduction of the lesion and recalcification. Radiographs (Fig. 4A and B) taken after four years showed the complete recalcification giving an appearance similar to the normal right tibia bone. Clinically the patient is now asymptomatic with a normal appearance of the left leg and normal function. Growth and development have been normal with no apparent sequelae or complication in the treatment area.

Case 2

A 12-year-old Hindu boy was seen in July, 1966, with pain and swelling in the right upper arm near the shoulder joint. Radiography (Fig. 5) revealed destruction of right upper humerus with a cystic appearance near the epiphysis, involving metaphysis and part of the diaphysis. A fusiform expanded lesion was located eccentrically in relation to the long axis of the shaft of humerus. On exploration a highly vascular unresectable lesion was found. The histopathology (Fig. 6) revealed a few slit like spaces containing red blood corpuscles and a loose stroma with a few giant cells showing the characteristic appearance of an aneurysmal bone cyst. The lesion was treated with cobalt 60 teletherapy by a pair of parallel opposed fields 9 × 7 cm delivering a mid-line tumour dose of 1600 rad in eight fractions over a period of eight months (one fraction of 200 rad per month). A radiograph (Fig. 7) taken just after completion of treatment revealed recalcification of the lesion with the normal bone growth displacing the cyst towards the middle of the shaft. Follow-up every six months revealed a gradual reduction of the lesion and recalcification. A radiograph (Fig. 8) taken after 18 months revealed almost complete recalcification of the lesion with normal bone growth. A radiograph (Fig. 9) taken 6½ years after therapy revealed no evidence of any lesion, with a normal radiographic bony pattern. The patient is now a 23-year-old medical graduate with a normal right arm.

Discussion

In a review of the literature, surgery seems to be the simplest treatment of choice where an aneurysmal bone cyst is easily accessible. However, the anatomical site as well as the highly vascular nature of the cyst may make surgical excision impossible. In this situation radiotherapy seems to be the treatment of choice, *e.g.* lesions in vertebral bodies, pelvis and near the epiphysis in long bones of children.

Dahlin *et al.* (1955) reported the effect of radiation therapy in some of 26 cases but no specific follow-up data were presented. Taylor (1956) reported cure of

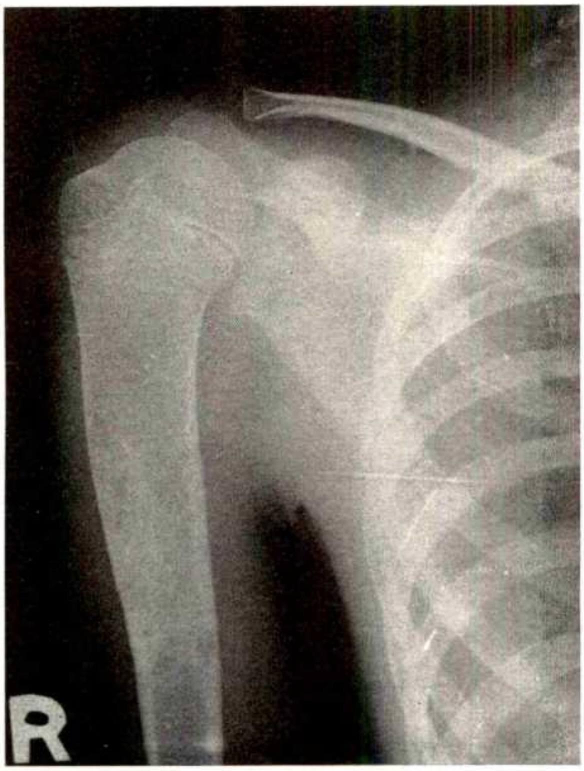


Fig. 8. *Case 2.*

Radiograph taken 18 months after completion of radiotherapy revealing displacement of the lesion towards the middle of the shaft with almost complete healing of the cyst.

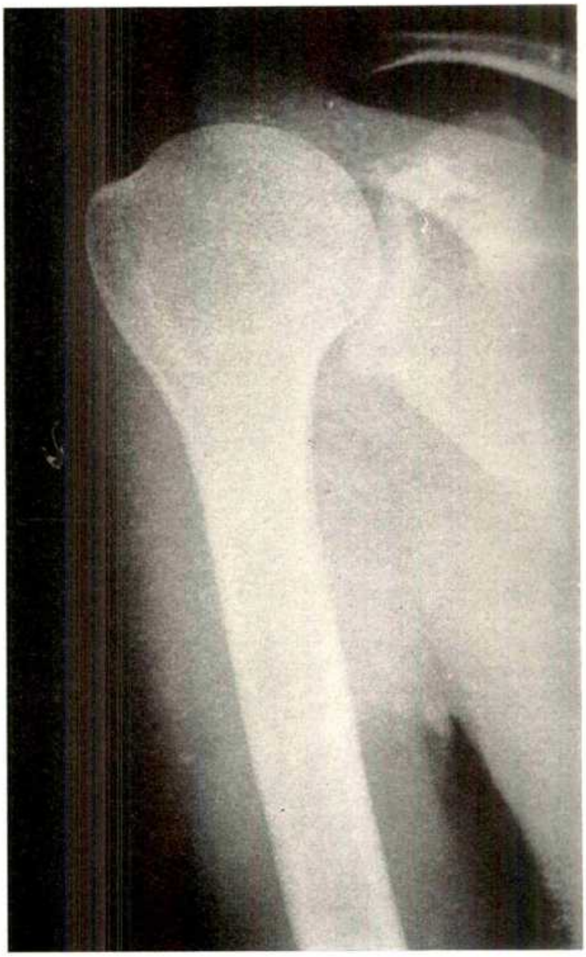


Fig. 9. *Case 2.*

Radiograph taken 6½ years after completion of radiotherapy showing normal appearance of the humerus with no evidence of the lesion.

two out of three patients by radiotherapy. Lichtenstein (1957) suggested the role of radiotherapy for lesions surgically inaccessible. Coley (1960) also recommended radiation therapy for lesions surgically inaccessible. Donaldson (1962) treated two cases successfully with irradiation and reported disease-free follow up periods of three and six years.

Nobler *et al.* (1968) studied 33 cases of aneurysmal bone cyst from 1923 to 1965 and found that the recurrence rate after surgery was about 32% higher than that after radiotherapy. They claimed the superiority of radiotherapy over surgery in a comparative study of the treatment of aneurysmal bone cyst by both modalities. Most of the earlier workers utilized deep X-ray therapy for the treatment of aneurysmal bone cyst with doses of the order of 1200–2500 rad in 10–20 days.

Recently Mark *et al.* (1976) have tried megavoltage irradiation with 4000 rad in four weeks and have demonstrated permanent control of the disease with good normal function. According to them a follow up of two years seems to be adequate, as recurrence is usually evident within six to 12 months after radiotherapy. The radiation may, however, cause the following adverse effects if delivered in high doses. 1. Arrest of bone growth. 2. Damage to surrounding soft tissue or organs. 3. Sarcomatous changes in the bone at a later time.

Bearing in mind the damaging effects of radiation to the growing bone we have utilized a lower range of radiation doses of cobalt 60 teletherapy. The interval between fractions was also prolonged from one week to one month to further reduce overall damaging effects of radiation and give ample time for the normal bone to recover. Even the low doses used by us in both of the cases treated with markedly prolonged treatment times (1400 rad in seven weeks and 1600 rad in eight months) have shown permanent cure of the lesions confirmed by the follow-up of four years and ten years respectively.

These results show the need for further studies to decide the optimum minimal dose and the duration of the interval between fractions required for the radiotherapeutic management of aneurysmal bone cysts. Such low doses, with prolonged intervals, are not expected to produce any adverse radiation effects on the growing bone of children and, in future, radiation treatment can be considered on these lines.

REFERENCES

Coley, B. L., 1960. *Neoplasm of bone and related conditions*, Ed. Paul B. Hoeber, pp.169–173 (New York).

Dahlin, D. C., Besse, B. E., Pugh, D. G., and Ghormley, R. K., 1955. Aneurysmal bone cysts. *Radiology*, *64*, 56–65.

Donaldson, W. F., 1962. Aneurysmal bone cysts. *Journal of Bone and Joint Surgery 44–A*, 25–40.

Jaffe, H. L., and Lichtenstein, L., 1942. Solitary Uni Cameral bone cyst with emphasis on the roentgen picture, the pathological appearance and the pathogenesis. *Archives of Surgery*, *44*, 1004–1025.

Lichtenstein, L., 1957. Aneurysmal bone cysts. Observations on 50 cases. *Journal of Bone and Joint Surgery*, *39–A*, 873–882.

Mark, R. D., Scruggs, H. J., Wallace, K. M., and Fen, J. O., 1976. Megavoltage therapy in patients with aneurysmal bone cysts. *Radiology*, *118*, 421–424.

Nobler, M. P., Higinbotham, N. L., and Philips, R. F., 1968. The cure of aneurysmal bone cyst. *Radiology*, *90*, 1185–1192.

Taylor, F. W., 1956. Aneurysmal bone cyst: report of 3 cases. *Journal of Bone and Joint Surgery 38–B*: 293–300.

Book review

CRC Handbook series in Clinical Laboratory Science. D. Seligson, Editor-in-Chief. *Section A: Nuclear Medicine Volume I*, Section Ed: R. P. Spencer, pp. 609, Illust., 1977. (CRC Press Inc., Ohio) £55·20.

This is a new addition to this series of handbooks which originally concentrated on chemistry and physics. The present volume is the first of the section devoted to nuclear medicine. It is a multi-author book which covers the skin, genital system, body composition and haematology, tumour scanning, reticuloendothelial and lymphatic systems, skeletal system and central nervous system. Like the other volumes the book presents most of its information in the form of tables, key references and a few illustrations. The material covered is exceptionally detailed and is much wider than one normally sees in text books of nuclear medicine, covering both animal and human data. Especially valuable are tables listing and summarizing the various techniques and pharmaceuticals used for imaging a particular area. These tables bring together references from a wider spread of papers than one would normally see.

Without doubt this book should be in all libraries which deal with the use of radioactive isotopes for diagnosis and research. It will also be valuable for physicians and surgeons who have only a more superficial interest in the subjects. It gives good information on the accuracy of the various techniques currently used in clinical medicine.

V. Ralph McCready

1978, *British Journal of Radiology*, *51*, 613–621

Implementation of the Philips treatment planning system for use in radiation teletherapy

By R. G. Dale, M.Sc., M.Inst.P.

Department of Medical Physics, Charing Cross Hospital, London W6 8RF.

(Received January, 1978 and in revised form March, 1978)

Abstract

The Philips TPS is a dedicated computer system primarily for the calculation and display of radiotherapy dose distributions resulting from multiple field and rotational beam teletherapy techniques. Although a comprehensive range of planning facilities is offered by the system, including calculations in a number of parallel slices taken through the patient, the amount of basic data required to program the system is modest. This paper describes the beam checks which are necessary in order to obtain the input data, and then examines how well the computed radiation beams compare with independently measured isodose distributions. Other features of the system are discussed and an assessment of its operational reliability is given. The recently developed interstitial program is not examined here.

The Philips treatment planning system (TPS) is a commercially available dedicated computer system for the calculation and display of radiotherapy dose distributions resulting from the use of megavoltage therapy equipment. The theoretical basis of the teletherapy beam programs has been described by Van de Geijn (1965, 1970, 1972) and this approach has been extended and improved for incorporation into the TPS. Because the method is based on the mathematical generation of isodose curves only a limited amount of data retrieval is required, in contrast to those systems involving matrix addition methods, the best example of which is the Rad 8 (Bentley and Milan, 1971; Milan and Bentley, 1974; Redpath *et al.*, 1977). At the time of the joint BIR/DHSS Consultant Study on Computerised Dose Computation (Barber, 1973), only one TPS had been supplied to a hospital user and little routine operational experience was available. Since then a number have been supplied to centres throughout the world, including one to this hospital in June 1976. This paper describes the physical measurements necessary to implement the system, together with an assessment of its accuracy and reliability following 18 months of operational experience.

General Description of System

The TPS has been built around a Philips P855 minicomputer with a 32K (16-bit word) core memory. Figure 1 shows a block diagram of the hardware. On the left of the diagram the means for input of information are symbolized. The cassette tape stores the semi-permanent data, primarily beam and machine data which are necessary for the calculation of dose distributions. The tape is made up by Philips using the information supplied to them by the user, one cassette being enough to store data for 12 treatment machines. The patient outlines, together with details of internal structures, are entered into the system by means of an ultrasonic pen which traces round a life-size drawing of the body cross-section mounted on the writing desk. During the input procedure the outlines of the various organs are automatically numbered in order that tissue densities may be assigned to each by the operator, if this is required. Up to nine body cross-sections from one patient may be entered in this way. If necessary, external structures such as couch tops may also be entered into the plan at this stage. All numerical information is fed in via a keyboard, each particular item of data entered being specified by means of indicator lights mounted on the front panel of the TPS. The planning steps follow logically from one another and at any stage the operator can ask for all the current beam parameters to be displayed simultaneously. Normally the entry sequence is selected by the computer, but the operator may skip directly to any previously specified parameter by pressing a push button adjacent to the appropriate indicator, should an alteration be required. This facility is an important part of the interactive process for effecting improvements in beam distributions. A separate keyboard is supplied for the input of patients' names and hospital numbers and a further set of buttons are provided for changing beam angles and positions.

On the right of Fig. 1 the means for output of information are shown. The storage display serves for visualization of graphical and alpha numeric information. The hard-copy unit connected to the storage display can produce an electrostatic print of the information on the screen at any time. Beam settings which are fed into the system by means of the various buttons are displayed on the main panel. A more detailed description of the design philosophy and operating procedure of the TPS has been given by Haarman *et al.* (1975) and Van de Geijn (1975).

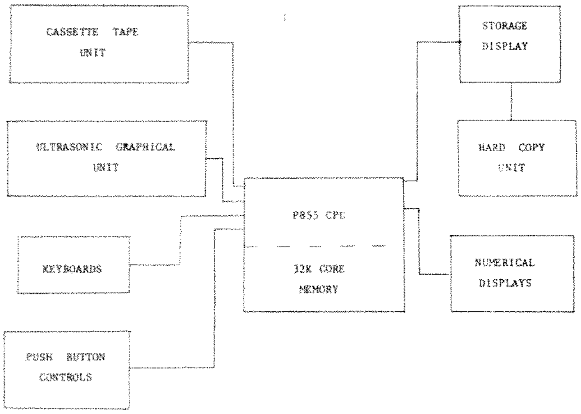


FIG. 1.
Block diagram of the TPS hardware.

Some clinical operating experience has been given by Rödel (1977).

The teletherapy program necessary for the dose computation is initially entered into the system by means of cassette tape and thereafter is stored. At the present time we have only the one program, although a comprehensive interstitial package may be supplied to all TPS users. A FORTRAN extension to the computer is available to centres who wish to develop their own programs.

MEASUREMENT OF DATA

All data relating to the treatment machines are collected together in the data acquisition book (DAB) supplied by Philips. The information collected in this way is compiled by the company and written onto the data cassette tape, which is then sent back to the users for acceptance checks. In the case of this hospital this tape stores data for two Mobaltron-80 ^{60}Co units; essentially the machines are identical except for their different source strengths.

The DAB contains all the necessary tabulation space for direct entry of the required data and is supplied with guide lines which explain the layout of the book and specify the desired format. In general the DAB is easy to follow, but requires detailed study prior to the physical measurements if duplication of effort and the necessity for repeat readings is to be avoided. In our case one person spent about a week studying the DAB; all the relevant measurements were then completed by two people, using a simple plotting tank, in about 20 hours (on one machine at two values of SSD and one SAD). The extraction of the required data from these readings and all the necessary cross-checks occupied about 60 man-hours, but this figure could probably have been reduced if an automatic dose plotter had been used for the basic measurements.

The TPS requires the following principal information for each treatment unit.

1. A general description of the therapy unit in terms of important distances and dimensions (*e.g.* SSD, source-filter distances, field size definition, etc.) and a specification of the modes of operation.

2. Peak dose rates for each square field size available (at 1 cm intervals) at each SSD and SAD. In the case of measurements for SAD techniques, the isocentric point has to be set at a distance of 10 cm beneath the water surface.

3. Percentage depth-dose data for a range of square field sizes at each SSD and SAD. The depths (in mm) at which specified percentile values occur are required for each field size. The number of field sizes to be investigated is not rigidly specified; we examined nine fields for each treatment distance. Depth-dose values for missing fields are generated by linear interpolation. It is allowable in the DAB to state depth-dose values at less than the peak build-up depth. We did not do this and so a surface dose of 30% of the maximum is assumed for all fields.

4. For the same square field sizes as covered in 3, profile data along a principal axis are required at 10 cm depth, normalized to a value of 100% on the central axis. The distances off axis of 16 specified percentile values are tabulated and, again, missing field data are generated by linear interpolation. For reliable results the profiles must be measured and not derived from existing isodose curves. Additionally, for the largest field available, a profile plot is required at the peak build-up depth. This is required to determine the differential scatter correction, which is a numerical way of dealing with the variations in the profile distributions with depth.

5. The physical dimensions of wedge filters and their supports are required, together with the relevant attenuation coefficients. If the wedges do not move with the beam-defining diaphragm, but occupy a fixed position relative to the beam axis, then this must be specified. No beam data measurements are required for any wedge field.

6. If rectangular filtering blocks can be used in the beam then profiles are required (at 10 cm depth) beneath each block along the major and minor axes, together with central axis depth-dose determinations. The measurement and subsequent manipulation of these data for entry into the DAB was found to be particularly time consuming as our TPS was being programmed to work with ten such blocks. At

present, our program cannot generate beams which incorporate blocks with tapered sides, but planning with such filters can be accomplished if the block shapes are entered into the system as external structures by means of the ultrasonic pen.

No significant problems were encountered in the compilation of data for the DAB and only one major copying mistake has been noted in the contents of data cassettes sent from Holland. This related to the radiation outputs of one of the treatment machines and, although a potentially serious error, it was quickly found in the checks made before releasing the tape for clinical use.

ASSESSMENT OF BEAM ACCURACY

After obtaining the basic data required for the TPS beam generation program, we were able to make use of the SHM automatic isodose plotter (by courtesy of the DHSS, London) in order to give us an independent check on our ^{60}Co distributions in water. A wide range of isodose curves, central-axis percentage depth doses and beam profiles were measured with the plotter and, on comparison with TPS generated data, the main points relating to the accuracy of the computer system were found to be as follows.

Central axis percentage depth doses

The TPS central-axis depth doses for all square fields are, as is to be expected, in very good agreement with measured depth doses. At the two principal treatment distances (80 cm SSD and 80 cm SAD) only the 90% depth-dose percentiles for small fields show measurable displacements, the biggest discrepancy being for the 4×4 cm field where the shift approaches 2 mm. At the longer treatment distance of 140 cm the agreement is nearly perfect for all except the very largest fields, where some of the lower percentile values on the TPS (*i.e.* those less than 50%) are displaced towards the surface by 1 or 2 mm.

Central axis depth doses for rectangular fields are generated by the TPS from the square field data, a table of equivalent squares (*British Journal of Radiology Supplement No. 11*, 1972) being incorporated into the computer program. At 80 cm SSD, for the fields of greatest elongation (*i.e.* 15×4 cm to 25×4 cm), there is a maximum discrepancy of 3 mm between the positions of measured and generated percentiles, such differences occurring at depths greater than 10 cm. For elongation factors of three or less the discrepancies are generally negligible. Some of the figures for intercomparison (at 80 cm SSD) have been collected together in Table I.

TABLE I

CENTRAL AXIS DEPTH DOSE DATA.

Field size (cm × cm)		90%	70%	50%	30%
4×4	Measured	24	59	102	167
	TPS	22	58	102	167
6×6	Measured	26	63	109	175
	TPS	24	62	109	175
8×8	Measured	26	66	115	184
	TPS	25	66	115	184
10×10	Measured	27	69	119	191
	TPS	27	69	119	192
15×15	Measured	29	75	130	208
	TPS	29	75	130	208
25×25	Measured	30	80	139	224
	TPS	30	80	139	224
7×4	Measured	23	61	105	170
	TPS	23	59	103	170
25×4	Measured	24	63	111	181
	TPS	24	65	114	184
15×7	Measured	27	68	118	190
	TPS	27	69	119	192
20×15	Measured	29	75	131	209
	TPS	28	75	132	209
25×30	Measured	29	79	136	218
	TPS	29	78	136	217

The table shows the depth (to nearest mm) in water at which the given percentile levels occur.

Beam profiles

The overall shape of the computed isodose curves is obviously most dependent on the accuracy with which off-axis factors at any point in a beam of radiation can be generated from profiles measured only at 10 cm depth. Before considering the discrepancies that have been found, it must be noted that individual radiation beams viewed on the TPS screen tend to have a "clipped" or angular appearance due to the effects of interpolation between the matrix elements.* The clipping effect is only particularly noticeable for the smaller field sizes; where two or more fields are added together in a treatment plan it is generally of much less significance. In order to overcome any possible anomalies arising from such sources, the off-axis data for the generated beams were obtained from the TPS using the so-called "dose-points" facility. Using this it is possible to position points within a radiation beam projected onto the screen, with a positional accuracy of ±1 mm, and to read off the doses at such locations. By positioning the points along a horizontal line and normalizing to a value of 100 on the central axis, it is possible to reconstruct from the screen beam profiles at any depth. Intercomparisons between measured and generated profiles have been made at depths of 2, 5, 10 and 15 cm. The off-axis factors at 10 cm depth for all square fields are found to be in complete agreement with our own measurements. Of the three other depths examined, the TPS is found to differ significantly from measured data only at the smallest depth, *i.e.* 2 cm. The magnitudes of the differences are quite small, as will be seen from Fig. 2, which shows profiles for three sizes of square field. It will be noted that the TPS points tend to be displaced towards the central axis for percentile values of greater than 80% and there is a tendency for them to be displaced outwards at the low percentile levels. At the other depths the results are qualitatively similar but such differences as do exist are equivalent to displacements of 1 mm or less. For the rectangular fields the results were exactly the same as for square fields. The program cassette tape originally supplied by Philips gave results which, although clinically acceptable, were in slightly poorer agreement with measurements than those reported here. This tape was replaced by a more accurate one by Philips as part of their routine update service.

---

*For large outlines the elemental spacing corresponds to 1 cm on the plan, but where the horizontal dimension is less than 25 cm, or the vertical dimension is less than 15 cm, the elements are spaced 5 mm apart.

It is an inherent feature of the Van de Geijn method of calculation that the beam calculations may be extended into the third dimension using basic data derived from two dimensional plotting (Van de Geijn, 1972). In order to assess the accuracy of dose distributions so derived, the SHM plotter was used to measure a limited number of isodose curves in those sections of radiation beams which are not normally examined. Figures 3 and 4 show direct comparisons between two such measured curves and their TPS counterparts. In Fig. 3, the section

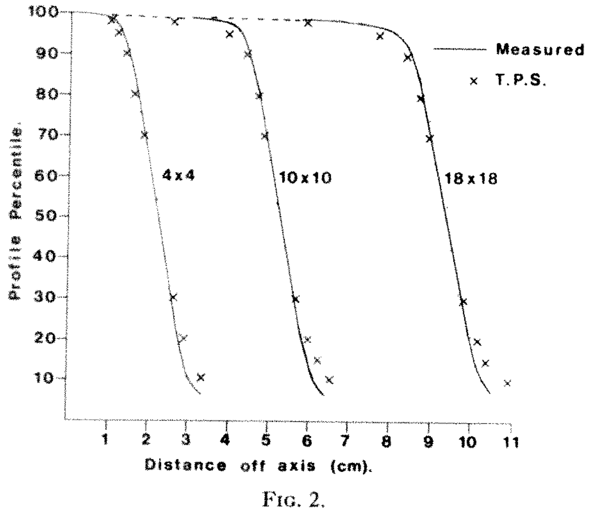


Fig. 2.

Beam profiles at 2 cm depth for square fields at 80 cm SSD.

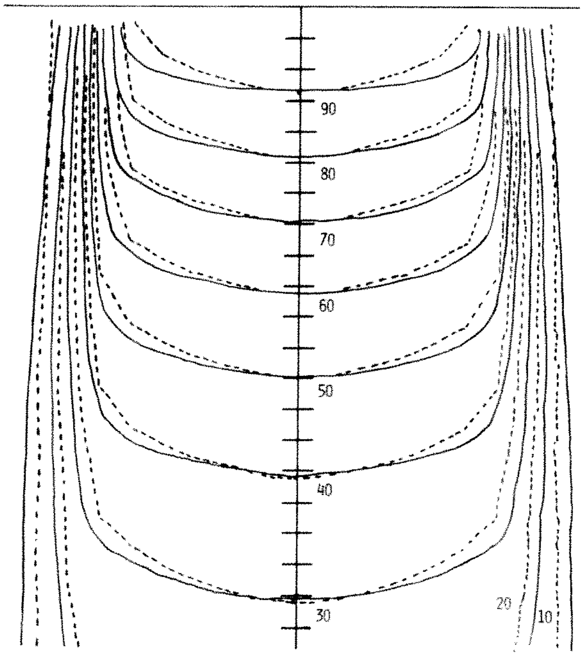


Fig. 3.

Isodose curves in the diagonal section of a 10 × 10 cm beam. Continuous curves are measured, dotted curves are from TPS.

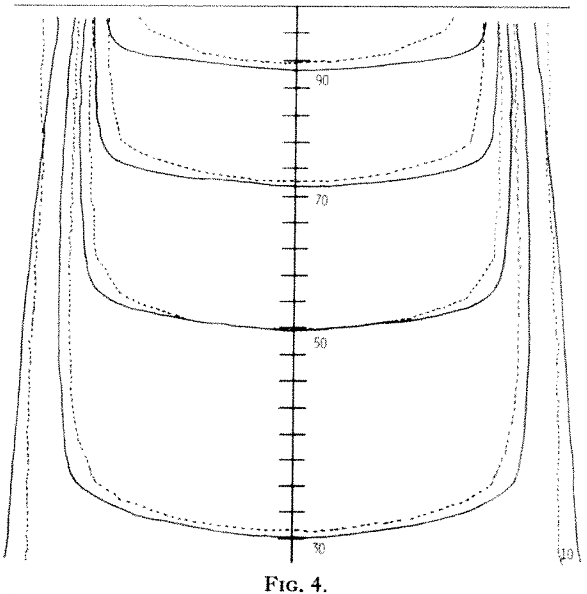


Fig. 4.

Isodose curves for a 15 × 15 cm beam in a vertical section 6 cm from a major axis. Continuous curves are measured, dotted curves are from TPS. Only alternate isodose levels were plotted.

viewed is that of the diagonal plane of a 10 × 10 cm field at 80 cm SSD. Figure 4 shows the isodose distributions for a 15 × 15 cm field as seen in a vertical section taken 6 cm away from, and parallel to, one of the principal axes. A number of such intercomparisons have been made for different field sizes with sections at varying distances off-axis. The discrepancies between measured and generated curves, when expressed in terms of percentage error in dose at any point, are generally small. In the "useful" part of the beam the dosage errors are less than 3% of the absolute dose at that point for nearly all the fields examined, even in sections which are well away from the central ray and which are approaching the edge of the beam. The overall width of the beam in off-axis sections tends to be underestimated by the TPS by as much as 2–3 mm at all depths, even for the smaller fields.

Wedged fields

It is the practice at this hospital to express wedge isodose levels in terms of the maximum dose in the unwedged field. In order to maintain this convention with the TPS, it is necessary to call wedged fields from the selection panel as "compensators" rather than "wedges", because TPS wedged fields are given a peak value of 100% at 5 mm depth on the central axis and renormalized to this figure. It would be possible to overcome this by assigning to each wedged field a beam weight which is numerically equal to the appropriate wedge factor, but this would involve cross reference to other tables during planning and the likelihood of human errors occurring would be increased. Thus, in all routine planning, the wedges are called from the program as compensators; the computer results presented here were obtained in the same way.

The central axis depth doses of the TPS wedged isodose curves are not in quite the same agreement with our plotted curves as was found to be the case with non-wedge fields, although in terms of doses delivered any differences noted are small and clinically insignificant. Table II summarises the results for the four field sizes investigated in greatest detail. No clear trend emerges from an analysis of the data, only the observation that the discrepancies tend to increase with increasing field size and wedge angle.

In order to check the shapes of computed curves fairly rigorously, cross-plots were obtained with the SHM plotter at depths of 0.5, 5, 10, 15 and 20 cm for 15 combinations of field and wedge. The results obtained indicate that the TPS wedge curves are

TABLE II

CENTRAL AXIS DEPTH DOSE DATA (WEDGED FIELDS).

Field size (cm × cm)			70%	60%	50%	40%	30%	20%	10%
4 × 4	30°W	Measured	26	50	73	100	139	189	
		TPS	30	53	76	105	140	194	
	45°W	Measured	22	45	69	96	133	182	
		TPS	20	43	67	96	135	185	
	60°W	Measured		24	52	81	119	170	
		TPS		30	56	85	120	173	
6 × 6	30°W	Measured	26	49	75	106	145	198	
		TPS	25	48	75	106	144	194	
	45°W	Measured		32	60	92	132	188	
		TPS		35	60	90	130	182	
	60°W	Measured			37	70	110	165	261
		TPS			40	70	110	164	262
10 × 10	30°W	Measured	7	36	66	100	144	200	
		TPS	6	37	68	100	144	200	
	45°W	Measured		6	43	79	123	181	
		TPS		6	45	76	120	177	
	60°W	Measured				33	79	142	240
		TPS				35	85	140	236
15 × 15	30°W	Measured		21	54	91	139	200	
		TPS		19	55	94	140	200	
	45°W	Measured				57	104	170	
		TPS				50	100	165	
	60°W	Measured					36	108	226
		TPS					30	100	236

The table shows the depth (to nearest mm) in water at which the given percentile levels occur.

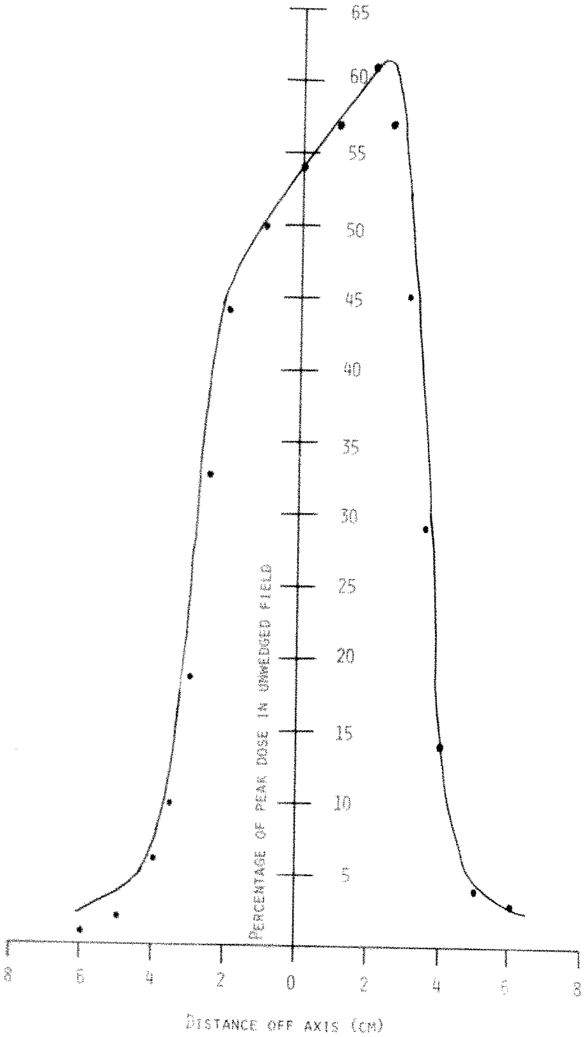


FIG. 5.
Measured beam profile for 6×6 cm beam with 45° wedge filter, at 80 cm SSD and 5 cm depth. The dots are TPS points.

basically reliable, although generally the computer isodose curves tend to become more narrow with depth than the measured curves. Figure 5 shows a profile for one field at 5 cm depth and indicates the differences which are typically observed. Figure 6 shows a direct intercomparison of the full field. It will be noted that beneath the thick end of the wedge there is a tendency for the TPS lines to be displaced about 2 mm towards the central axis.

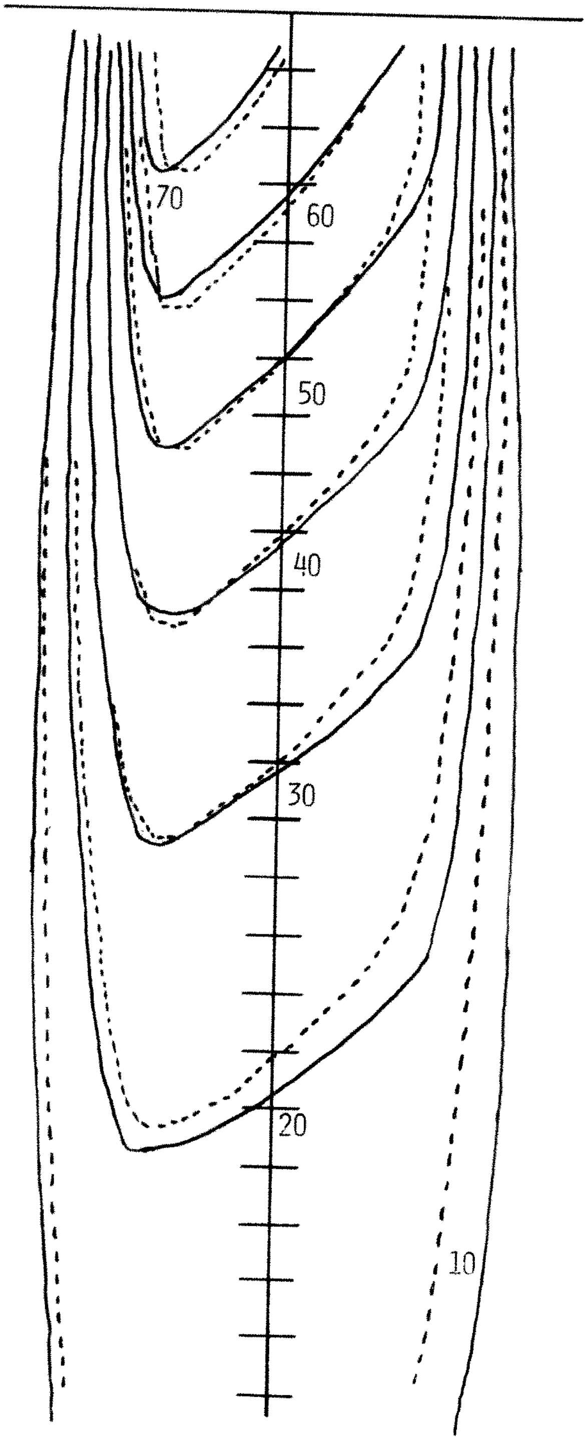


FIG. 6.
Isodose curves for a 6×6 cm beam with 45° wedge filter. Continuous curves are measured, dotted curves are from TPS.

OTHER ASPECTS RELATING TO ACCURACY

Calculation of treatment times and corrections for source decay

Treatment time calculations are based on the peak dose rates for square fields specified by the user on a given base date. These are automatically corrected for source decay to the date given on the treatment plan. Times for rectangular fields are calculated by the equivalent square method. For the most part the differences between computer-calculated and treatment-chart times are less than 0.2% for any chosen treatment date; for fields of extreme elongation this error may rise to a maximum of 1.2%.

Variable SSD feature and corrections for oblique incidence

The TPS will allow the operator to change the SSD of a fixed beam by up to 10 cm from its nominal value. Thus in our case fields may be set up with SSD in the range 70 to 90 cm, or 130 to 150 cm. The corrections for variations in SSD are applied in the computer by deriving the appropriate tissue air ratios (TAR) from the measured data by removing the inverse-square factor and introducing the back-scatter factor.

The values of TAR so derived, being virtually independent of SSD, are then used to calculate the depth dose curves at the actual SSD selected. For the range of SSD available and for a range of depths and field sizes, the TPS percentage depth doses have been compared with figures calculated, first by the above method and then by application of the $\frac{1}{2}(1+F^2)$ formula taken from *British Journal of Radiology, Supplement No. 11* (1972). The differences found in the intercomparisons can be ascribed mostly to rounding-off of the TPS figures. For irregularly shaped patient outlines the TPS calculations follow in principle the method described above, the SSD of any site being the distance from the source along the appropriate decrement line. For oblique incidence up to 45° the computer was found to give results which were in good agreement with the 2/3 isodose shift method (ICRU, 1963).

Exit dose errors

Because the TPS assumes that all beams are generated in an infinite phantom, it is to be expected that exit doses will be overestimated by an amount which depends on the field size and the patient thickness. In order to assess the magnitude of this effect check measurements have been made with an ionization chamber in slabs of Temex phantom material, the results being tabulated in Table III.

TABLE III

ERRORS IN EXIT DOSES

	Square field size (cm × cm)				
Tissue thickness (cm)	4×4	7×7	10×10	15×15	20×20
4	5.6	5.8	6.1	7.0	8.3
7	5.7	6.0	6.6	7.7	8.9
10	5.8	6.4	7.0	8.3	9.7
15	5.9	6.5	7.2	8.6	10.2
20	6.0	6.7	7.5	9.1	10.8

The figures give the percentages by which the exit dose is overestimated by the TPS.

For a parallel opposing field arrangement the net error in the determination of skin dose is dependent also on the true surface dose delivered by each incident beam. If the skin dose delivered by the beam is 30% of the peak dose (this is the figure assumed by the TPS), then the net error is about half that noted in the table.

Heterogeneity corrections

The TPS program treats heterogeneities by considering the effective depth, d_{eff}, of the various calculation sites (Van de Geijn, 1972), where

$$d_{eff} = \sum_i d_i \, q_i$$

where d_i is the path length in the i^{th} inhomogeneity of density q_i. For high energy radiations, where Compton interactions predominate, such an approach is justified provided only the changes in beam attenuation are considered. Since an increase in transmission will imply a decrease in the scatter contribution and vice versa, any tissue densities specified by the operator for use in the TPS need to be corrected to make allowance for such effects if doses to tissues beyond the inhomogeneity are to be correctly computed.

In clinical terms such corrections to the physical densities are only of real significance in the case of lung tissue, since bony structures in treatment plans are rarely more than 3 cm across. Several investigators have examined the problem of lung corrections (*e.g.* Greene and Stewart, 1965; Young and Gaylord, 1970), and based on their results a lung correction factor of 0.45 for 4MV X-rays has been suggested by Wilkinson and Redmond (1975). For the present work it was decided to make some check measurements in Temex phantoms containing slabs of cork (density 0.28) to simulate lung tissue. This value for the mean density of lung has been suggested by Fowler and Young (1959). The measured depth doses were then compared directly with figures from the TPS, the latter being obtained by positioning "dose-points" at appropriate sites in an identical phantom projected onto the screen. When the density of the cork was specified as being 0.28 the computer was found to give consistently high depth doses for points beyond the inhomogeneity. This was invariably true for a range of field sizes and a number of phantom configurations, the TPS figures being as much as 8% too high. By specifying an increased density for the inhomogeneity the computer was found to give better results, as expected, and the optimum value was found to be 0.4, for which the TPS usually agreed with measured values to within ±1.5%. This "trial and error" approach is a procedure which may be used with the TPS to find the optimum density for any inhomogeneity for which experimental results are available. In common with most other radiotherapy computers, the TPS does not allow for the short range effects which occur in the vicinity of interfaces where there is a lack or excess of scatter.

Optimization

In order to make use of the optimization facility in an attempt to improve an existing plan, the operator needs to specify the position of a reference point (which will usually be close to the beam intersections) together with three other points, referred to as "85% points" on the selection panel, which will normally be sited at the periphery of the treated volume. The TPS will then examine the effects of varying the beam weights and field widths (in that order) of the applied fields until an arrangement is found whereby the specified criterion is fulfilled, *i.e.* the three peripheral sites each receive at least 85% of the dose received at the reference point. Such a form of optimization (which only operates for static fields) is clearly of very limited applicability since it takes no account of high doses to critical structures, neither does it attempt to introduce beam filters or change field positions. In practice such drawbacks are of little consequence in the TPS since computerized optimization of a plan is never required on account of the high degree of interaction possible with the system.

DISCUSSION

The TPS will already cope with most of the techniques met with in the practice of megavoltage radiotherapy, and the latest program update, now ready for release, incorporates an impressive irregular field program for application to mantle techniques. Modification of the beam programs by the user is almost impossible and therefore the update service is a useful feature which is not offered by other manufacturers. The programs supplied have proved to be reliable as they stand, and it is difficult to find any serious criticisms of the planning accuracy of the TPS. It would be a distinct advantage if it were possible to store previously completed plans in the computer, but at present only the most recent plan is retained by the core. As a dedicated radiotherapy computer the TPS appears to be based on a sound design philosophy. This is reflected by the fact that it is regarded by radiotherapy staff more as a piece of therapy equipment than computer hardware and, because of this, the amount of time required to learn how to operate the system to its best advantage is quite small. The small size of the TPS and its quiet running are additional advantages in a department where space is at a premium. During the 18 months since its installation, the computer has only been out of action twice, once because of a burnt-out resistor and once for a sticking micro-switch. On each occasion the fault was rectified within 24 hours of it being reported to the company.

Although the physics staff at this hospital have no previous experience of commissioning a radiotherapy computer, it is believed that the amount of work required to implement the TPS compares favourably with that required for some of its rivals. Most people acquiring the computer will want to spend some time checking the system accuracy to their own satisfaction, particularly as the amount of raw data required to program the TPS is relatively small. Such checks will probably involve more time than it takes to measure the basic data, but it has been our experience that the use of the computer for routine planning need not be delayed until all such checks are completed.

ACKNOWLEDGMENTS

The author wishes to thank Dr. N. W. Ramsey and Mr. D. Bradley for their interest and help in this project, and Mr. A. J. Stacey for discussions and advice relating to the tissue equivalence of lung phantoms. The encouragement provided by Dr. D. O'Connell and Miss K. A. Jones is also gratefully acknowledged. The support provided by Philips Medical Systems has proved invaluable, and particular thanks are due to Mr. D. R. Hill, Mr. J. Davies, Dr. P. A. M. Van Overbeek and Dr. J. Lammerts.

REFERENCES

Barber, B., 1973. *Computerised Dose Computation.* A report prepared for the British Institute of Radiology and the Department of Health and Social Security, London. (Unpublished)

Bentley, R. E., and Milan, J., 1971. An interactive digital computer system for radiotherapy treatment planning. *British Journal of Radiology*, *44*, 826–833.

British Journal of Radiology, Supplement No. 11 (1972). Central axis depth dose data for use in radiotherapy.

Fowler, J. F., and Young, A. E., 1959. The average density of healthy lung. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 81, 312–315.*

Greene, D., and Stewart, J. G., 1965. Isodose curves in non-uniform phantoms. *British Journal of Radiology, 38,* 378–385.

Haarman, J. W., van Leiden, H. F., and Pruis, D., 1975. An interactive three dimensional treatment planning system. *Medicamundi, 20,* 23–32.

International Commission on Radiological Units and Measurements, (1963). Clinical Dosimetry (Report 10d). (Washington, N.B.S. Handbook 87).

Milan, J., and Bentley, R. E., 1974. The storage and manipulation of radiation dose data in a small digital computer. *British Journal of Radiology, 47,* 115–121.

Redpath, A. T., Vickery, B. L., and Duncan, W., 1977. A comprehensive radiotherapy planning system implemented in Fortran on a small interactive computer. *British Journal of Radiology, 50,* 51–57.

Rödel, K., 1977. Experience with a therapy planning system in clinical routine. *Medicamundi, 22,* 39–47.

Van de Geijn, J., 1965. The computation of two and three dimensional dose distributions in Cobalt-60 teletherapy. *British Journal of Radiology, 38,* 369–377.

1970. A computer program for 3-D planning in external beam radiation therapy, EXTDΦS. *Computer Programs in Biomedicine, 1,* 47–57.

1972. EXTDΦS71. Revised and expanded version of EXTDΦS, a program for treatment planning in external beam therapy. *Computer Programs in Biomedicine, 2,* 169–177.

1975. Evaluation of the Philips treatment planning system. *Medicamundi, 20,* 125–132.

Wilkinson, J. M., and Redmond, W. J., 1975. Experience in implementing the Mark III Rad8 system for radiotherapy dose computations. *British Journal of Radiology, 48,* 732–738.

Young, M. E. J., and Gaylord, J. D., 1970. Experimental tests of corrections for tissue inhomogeneities in radiotherapy. *British Journal of Radiology, 43,* 349–355.

Book reviews

Acoustic instrumentation and characterisation of lung tissue. By T. L. Rhyne. Ultrasound in Biomedicine Series, Vol. 2, p. 107, 1977 (Forest Grove, U.S.A; Research Studies Press), $14.95.

Ultrasound has hitherto been largely discounted for investigations of the lung, on the grounds that the surface of aerated lung constitutes an almost perfect barrier to sound propagation. Various disease conditions, however, such as emboli and emphysema may modify the surface properties in a manner that is sufficiently characteristic to lead to identifiable changes in the reflected ultrasonic energy. This subject has recently been investigated in a doctoral student project and the present monograph is a lightly edited version of the resulting thesis. Although it suffers from many of the afflictions common in such works—poor perspective, rediscovery of wheels, sparseness of experimental data (trials on three subjects only, all of which were normal) and erratic English—it nevertheless makes some useful contributions to the engineering aspects of the subject and serves as a reminder that the approach could be well worth a proper clinical trial. It also serves to prompt its reviewer to reconsider the curious status of doctoral theses. A major criterion for their acceptability is that they should contain publishable material and, whilst most presumably do get published in part, many must contain a good deal more that would be useful to a limited readership even though, as in the present instance, the thesis is unsuitable for publication in full. Perhaps some enterprising journal, such as The British Journal of Radiology, might consider publishing, in the form of abstracts prepared if possible by someone other than the author, a periodical selection of "recent dissertations in radiological science", and subsequently arranging for supply of microfilm copies of the original thesis.

C. R. Hill.

Introductory physics of nuclear medicine. By Ramesh Chandra, pp. 186, 1976 (Lea & Febiger, Philadelphia: distributed in UK by Henry Kimpton, London), £7·80.

The establishment of Nuclear Medicine as a speciality in its own right has undoubtedly been assisted by the recognition that the necessary background knowledge and skills are not those which can easily be "picked up on the job". Formal teaching of the physical and technical principles on which the speciality is based has, therefore, become a necessary part of training for both clinical specialists and the technicians on whom they may depend. This volume provides a compact textbook designed to satisfy the needs of such teaching.

The text requires a minimal scientific and mathematical background and proceeds in an orderly way to develop and explain the concepts required. It is particularly well set out and indexed, with clear and informative diagrams. Although concise, the contents are often too substantial to be readily digested at a first or even a second reading.

It covers most of what is likely to be required, although exposure dose and the calculation of protection requirements are notable omissions. The depth of discussion is generally adequate with a particularly good chapter on the interaction of radiations with matter. Some topics, however, such as semiconductor detectors, are dealt with so briefly that little understanding can be derived from the text alone.

This volume generally provides a physical foundation from which the reader may be expected to progress to original scientific papers. It could well assist in the understanding of any introductory course of lectures on the subject and thereafter provide a handy source of elementary reference.

M. F. Cottrall.

1978, *British Journal of Radiology*, *51*, 622–627

Mean skeletal dose factors for beta-particle emitters in human bone. Part I: volume-seeking radionuclides

By F. W. Spiers, C.B.E., D.Sc., Ph.D., F.Inst.P., A. H. Beddoe,* M.Sc., Ph.D., M.Inst.P., and Joan R. Whitwell, Ph.D.

Bone Dosimetry Research Unit, Department of Medical Physics, University of Leeds, Cookridge Hospital, Leeds

(*Received November, 1977 and in revised form January, 1978*)

ABSTRACT

Based on calculations by Whitwell and Spiers, mean skeletal dose factors for β-particle emitters have been derived for application to dosimetry in nuclear medicine, radiobiology and radiation protection. The dose factors apply to bone-seeking radionuclides that are deposited more or less uniformly throughout the human mineralized skeleton and are defined as: (1) ${}_{\mathrm{V}}\bar{D}_{\mathrm{M}}/D_{\mathrm{B}}$, the mean dose to the haemopoietic marrow in trabecular bone as a fraction of the "dose to bone", D_{B}; (2) ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$, the mean dose to endosteal (osteogenic) tissue lying in a zone 0–10 μm from trabecular surfaces, also as a fraction of the dose D_{B}.

Dose factors are given for three ages, 1.7, 9 and 44 years and for eight radionuclides, ranging in mean β-particle energy from 0.05 MeV (^{14}C) to 0.93 MeV (^{90}Y). Dose factors, calculated for a single lumbar vertebra of an infant aged 3.5 weeks, enable approximate values of mean skeletal dose factors to be estimated for ages less than 1.7 years. Limited data are also reported on dose factors for the femoral cortex from subjects aged 9 and 50 years.

There is evidence to show that the tissues in bone relevant to the risks of late irradiation effects in man are: (1) haemopoietic cells and other mesenchymal elements present in bone marrow; (2) endosteal cells lying close to bone surfaces in trabecular bone; and (3) the particular case of epithelial cells close to bone surfaces in the air sinuses of the skull (ICRP 1968, 1977; Vaughan, 1973). In this paper the results of dosimetric calculations are given for the tissues specified in (1) and (2); the results given for (2) may also apply, at least approximately, to the case of the epithelial tissues in (3). Furthermore the results presented here are also relevant to the clinical use of radionuclides; in diagnostic applications both the bone-marrow dose and the endosteal tissue dose should be known in relation to suggested dose limits; in radionuclide therapy the dose to bone marrow, for example, may either be determinant, as in treatment by ^{32}P (Spiers *et al.*, 1976), or limiting, as in some therapeutic uses of ^{131}I.

A Monte Carlo method for calculating β-ray dose factors (Whitwell and Spiers, 1976) has been applied to obtain the required factors for the human skeletal tissues concerned. They are expressed, however, as ratios of the mean absorbed tissue dose-rate to the conventional "absorbed dose-rate to bone", calculated as the energy released by the retained radionuclide burden divided by the total mass of the mineral bone. The notation used is that suggested by Marshall *et al.*, (1974); the dose factors for bone marrow and endosteal surfaces are designated as ${}_{\mathrm{V}}\bar{D}_{\mathrm{M}}/D_{\mathrm{B}}$ and ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$ respectively in the case of volume-seeking radionuclides. The mean skeletal values of ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$ relate specifically to the endosteal tissues lying within a zone 0–10 μm from the trabecular surfaces (ICRP, 1977). The data on cortical bone are insufficient for the determination of mean skeletal dose factors, but a few values of ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$ are given for the femoral cortex to indicate their general order of magnitude.

The data presented have been based on the measurement of trabecular bone structure in post-mortem specimens from three male subjects, aged respectively 1.7, 9 and 44 years, whose deaths were due to causes other than diseases involving possible bone changes. Measurements of structure have also been made on the lumbar vertebra (LV3) of a child of only 3.5 weeks (full-term gestational period) and this has enabled us to make approximate extrapolations of the mean skeletal dose factors for ages below 1.7 years.

CALCULATION OF MEAN SKELETAL DOSE FACTORS

Dose factors have been calculated for the trabeculation in the following bones: parietal bone, 7th rib, 5th cervical vertebra, 3rd lumbar vertebra, iliac crest, head of femur and neck of femur in the case of the adult, and for similar though not identical sets of bones of the children aged 1.7 and 9 years. Correction factors were then applied to allow for the escape of β-particle energy when the β-particle ranges exceeded the dimensions of the individual bones. Additions were also made to allow for a contribution to the dose from the presence of the radionuclide in the cortical shell, where this was appreciable. The dose factors have been calculated for the β particles of eight radionuclides of interest in clinical and radiation protection work.

The values of ${}_{\mathrm{V}}\bar{D}_{\mathrm{M}}/D_{\mathrm{B}}$ and ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$ for the individual bones have been used to calculate weighted skeletal average dose factors for the haemopoietic marrow and the endosteal cell layer (0–10 μm) adjacent to the trabecular surfaces. The weighting factors for the bone marrow, f_M, and for the bone surfaces, f_S, for the three ages 1.7, 9 and 44 years, are given in Table I where the bones of the whole skeleton are grouped according to site and structure The factors f_M are the fractional masses of active marrow in the bone groups and the factors f_S are the corresponding fractions of the total trabecular area.

---

*Present address: Department of Clinical Oncology, Auckland Hospital, Auckland, New Zealand.

The bone-marrow fractions for the 44 year adult have been derived (Whitwell, 1973) from the total marrow data of Mechanic (1926) multiplied by the cellularity fractions from Custer (1949) and normalized; they are close to the values given by Ellis (1961). The fractions for the two lower ages have been calculated by assuming that the relative distribution of the total marrow is the same as in the adult and applying cellularity fractions according to age from the date of Custer (1949). In the case of the 1.7 year child and approximate figure has also been included for the amount of marrow, all of which is assumed to be active, in the shafts of the long bones.

The weighting factors, f_S, for the endosteal dose factors have been derived from the bone marrow fractions, f_M. The relative surface area, A_{rel}, in a given bone is calculated from the formula:

$$A_{\text{rel}} = \frac{f_M}{p} \times \frac{V_B}{V_M} \times \frac{S}{V_B} \quad . \quad . \quad (1)$$

where:

p = cellularity fraction = mass-ratio active marrow/total marrow.

V_B/V_M = ratio of volume of trabecular bone to volume of marrow.

S/V_B = ratio of surface area to trabecular bone volume.

Normalized values of A_{rel} then give the values of f_S.

Each group of bones in column 1 of Table I is represented by one of the measured bones which has a trabecular structure approximating to the group as a whole: in some cases more than one bone is used to characterize the group. The skeletal average marrow dose factor is then $\Sigma f_M\ {}_V\bar{D}_M/D_B$ summed over all the groups of bones in Table I for each age. Simliarly, $\Sigma f_S\ {}_V\bar{D}_S/D_B$ gives the value of the skeletal average for all endosteal tissues in the zone 0–10μm adjacent to trabecular surfaces.

MEAN SKELETAL DOSE FACTORS FOR AGES 1.7, 9 AND 44 YEARS

Mean skeletal values of ${}_V\bar{D}_M/D_B$ and ${}_V\bar{D}_S/D_B$ are given in Table II for the three ages 1.7, 9 and 44 years for which bone structural measurements have been made. They are given for the β-particle energy spectra of eight radionuclides ranging in mean energy from 0.050 MeV to 0.927 MeV. In Figs. 1 and 2 the data for ${}_V\bar{D}_M/D_B$ and ${}_V\bar{D}_S/D_B$ respectively are plotted against the mean β-particle energy $\bar{E}_\beta$, so

TABLE I

WEIGHTING FACTORS FOR CALCULATING MEAN SKELETAL DOSE FACTORS

Groups of bones	Bone representing the group	Age 1.7 years		Age 9 years		Age 44 years	
		f_M	f_S	f_M	f_S	f_M	f_S
Cranium	PB	0.062	0.148	0.074	0.159	0.126	0.225
Mandible, ribs sternum	Rib.7	0.218[1]	0.231[1]	0.104	0.075	0.118	0.078
Cervical vertebrae	CV 5	0.193	0.155	0.021	0.015	0.036	0.030
Thoracic vertebrae	0.5 CV 5[2] +0.5 LV 3			0.088	0.063	0.151	0.114
Lumbar vertebrae and sacrum	LV 3			0.121	0.089	0.207	0.135
Clavicles, hip scapulae	0.6 IC[2] +0.4 LV 3	0.148	0.134	0.178	0.144	0.302	0.212
Long bones and extremities (trabeculation)	F head,[2] neck, and prox. third of shaft	0.308[3]	0.324[3]	0.414	0.455[4]	0.060	0.206[4]
Long bones (shafts)		0.0715	0.008[5]	—	—	—	—

Notation: PB = parietal bone, CV = cervical vertebra, LV = lumbar vertebra, IC = iliac creast, F = femur.

Notes:

[1] Includes extremities in this case.

[2] In these cases individual calculations have been made for separate bone sites, depending on subject, and then summed.

[3] Excludes extremities in this case.

[4] Includes small amount of trabecular surfaces in shafts.

[5] Calculated on the assumption that 19% of marrow in the long bones is in the shafts, *i.e.* in regions where there is little trabecular bone; the percentage is an approximate estimate from radiographs.

that values for other radionuclides can be obtained by interpolation. On both graphs mean skeletal dose factors are also given for an infant aged 0.067 year; these data are only approximate and are derived in the next section.

VARIATION OF MEAN SKELETAL DOSE FACTORS WITH AGE

The data in Table II show that there is a small trend with age in the mean skeletal values of $_{\mathrm{Y}}\bar{D}_M/D_B$ and $_{\mathrm{Y}}\bar{D}_S/D_B$. A similar trend is also found in the values of the dose factors for the lumbar vertebra listed in Table III. In this case the age range is extended down to 0.067 year by the measurements of structure made on a vertebral body of an infant aged 3.5 weeks. Examples of the trend with age are shown in Fig. 3 (for the radionuclides ^{14}C, ^{18}F, and ^{32}P), where the values of $_{\mathrm{Y}}\bar{D}_M/D_B$ for four lumbar vertebrae are plotted against age. Mean skeletal values of the dose factor are also plotted for the three older subjects. The curves for the mean skeletal factors run sufficiently parallel to those for the lumbar vertebrae to justify extrapolation to be made below the age of 1.7 years; this has also been done for the pairs of curves for the other radionuclides. The data for the endosteal surface dose factors have been used similarly to make extrapolations of the mean skeletal values of $_{\mathrm{Y}}\bar{D}_S/D_B$; in this case the curves for the mean skeletal values lie very close to those for the lumbar vertebrae and the basis for extrapolation is more certain. As a result, mean skeletal dose factors for the age 0.067 year are included in Figs. 1 and 2 as well as the directly calculated factors for the other ages.

Lastly the data of Figs. 1 and 2 have been recast to give the variation with age of the mean skeletal dose

TABLE II

MEAN SKELETAL DOSE FACTORS FOR EIGHT β-PARTICLE EMITTERS FOR SUBJECTS AGED 1.7, 9 and 44 YEARS

Dose factor	Age (years)	Radionuclides and mean β-particle energies (MeV)							
		^{14}C 0.050	^{45}Ca 0.077	^{90}Sr 0.200	^{22}Na 0.218	^{18}F 0.253	^{90}Sr+^{90}Y 0.564	^{32}P 0.695	^{90}Y 0.927
$\frac{_{\mathrm{Y}}\bar{D}_M}{D_B}$	1.7	0.088	0.156	0.297	0.304	0.324	0.404	0.404	0.404
	9	0.077	0.138	0.266	0.269	0.288	0.350	0.346	0.357
	44	0.064	0.124	0.264	0.264	0.285	0.357	0.363	0.367
$\frac{_{\mathrm{Y}}\bar{D}_S}{D_B}$	1.7	0.439	0.492	0.502	0.512	0.510	0.474	0.475	0.451
	9	0.433	0.486	0.478	0.481	0.479	0.447	0.446	0.419
	44	0.429	0.489	0.485	0.488	0.482	0.451	0.448	0.435

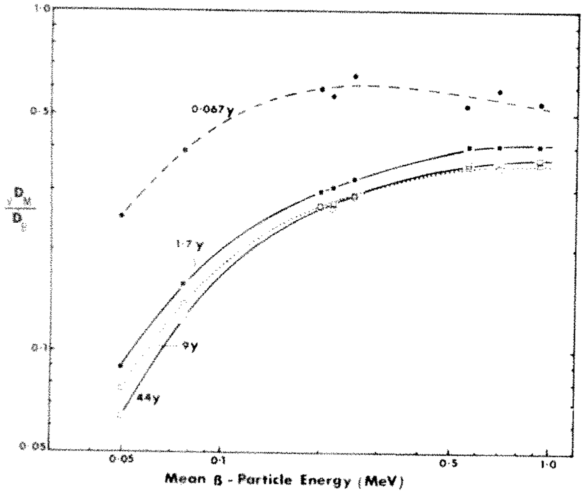


FIG. 1.

Variation of mean skeletal dose factors for marrow, $_{\mathrm{Y}}\bar{D}_M/D_B$, with mean β-particle energy.

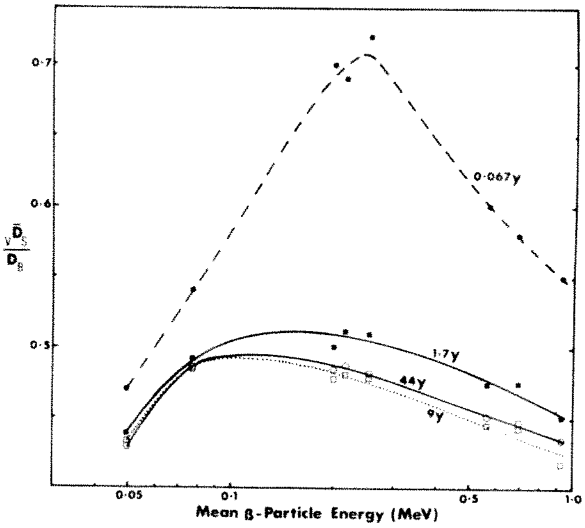


FIG. 2.

Variation of mean skeletal dose factors for endosteal surfaces. $_{\mathrm{Y}}\bar{D}_S/D_B$, with mean β-particle energy.

TABLE III

DOSE FACTORS FOR THE LUMBAR VERTEBRAE OF HUMAN SUBJECTS AGED 0.067, 1.7, 9 and 44 YEARS

Dose factor	Age (years)	Radionuclides							
		^{14}C	^{45}Ca	^{90}Sr	^{22}Na	^{18}F	^{90}Sr + ^{90}Y	^{32}P	^{90}Y
${}_{\mathrm{V}}\bar{D}_{\mathrm{M}}/D_{\mathrm{B}}$	0.067	0.219	0.343	0.489	0.495	0.502	0.405	0.437	0.378
	1.7	0.0767	0.136	0.248	0.252	0.265	0.285	0.297	0.288
	9	0.0652	0.116	0.188	0.190	0.203	0.237	0.245	0.242
	44	0.0469	0.089	0.185	0.186	0.202	0.248	0.255	0.259
${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$	0.067	0.461	0.518	0.548	0.553	0.548	0.418	0.446	0.384
	1.7	0.428	0.455	0.405	0.410	0.398	0.329	0.334	0.312
	9	0.413	0.445	0.375	0.381	0.365	0.296	0.294	0.277
	44	0.415	0.450	0.386	0.392	0.377	0.316	0.313	0.299

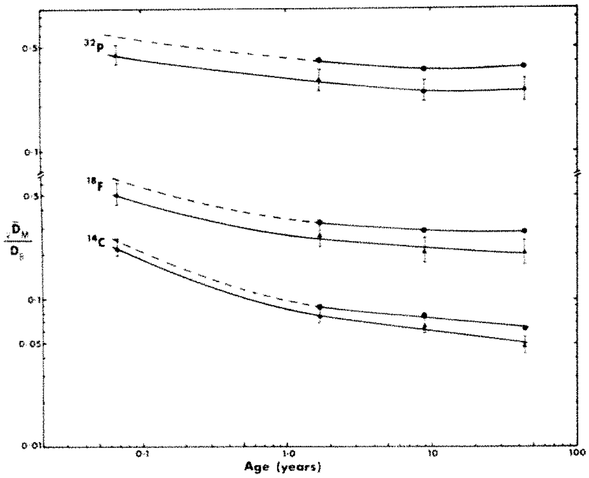


FIG. 3.

Variation with age of (a) mean marrow dose factors for the lumbar vertebra LV3 (▲) and (b) mean skeletal dose factors for marrow (●). Error bars shown for LV3 are standard deviations calculated for eight adult lumbar vertebrae to indicate expected variation. Extrapolation shown by dashed line.

factors ${}_{\mathrm{V}}\bar{D}_{\mathrm{M}}/D_{\mathrm{B}}$ and ${}_{\mathrm{V}}\bar{D}_{\mathrm{S}}/D_{\mathrm{B}}$ at specific mean β-particle energies from $\bar{E}_\beta = 0.05$ MeV to $\bar{E}_\beta = 1.0$ MeV, as given in Figs. 4 and 5.

DOSE FACTORS FOR CORTICAL BONE

Dose factors have also been calculated for a layer of cells lying within 10 μm of the surfaces of cavities in human cortical bone. They are based on measurements of path lengths (a) through Haversian canals and resorption cavities, and (b) through the intervening bone, in a limited number of specimens of cortical bone (Beddoe, 1977). Variation in the structure of cortical bone between different bones of the skeleton is much less than in the case of trabecular bone, but insufficient data are available for the derivation of mean skeletal dose factors. Nevertheless,

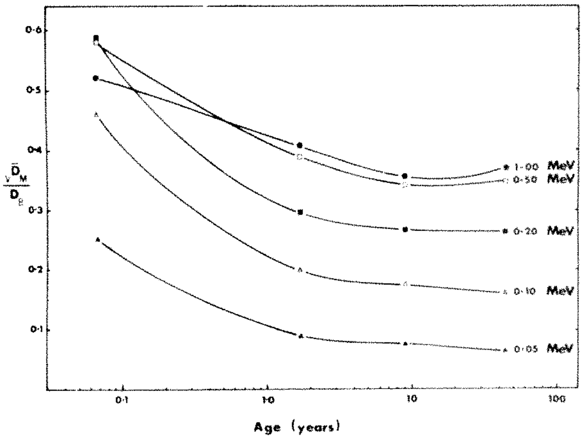


FIG. 4.

Variation with age of the mean skeletal dose factors for marrow, for five selected mean β-particle energies.

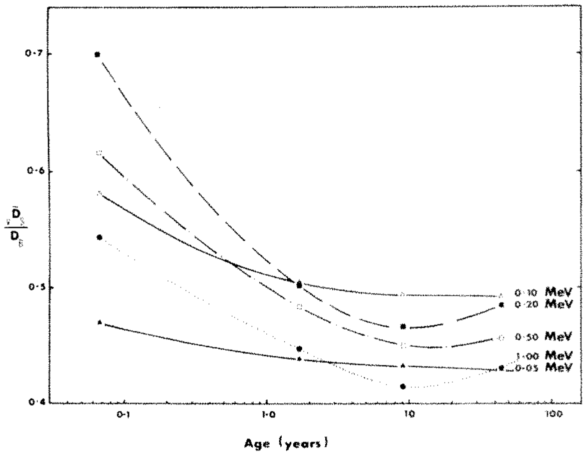


FIG. 5.

Variation with age of the mean skeletal dose factors for endosteal tissues, for five selected mean β-particle energies.

TABLE IV

DOSE FACTORS, v$\bar{D}_S/D_B$, FOR FEMORAL CORTEX (MALE CHILD, 9 YEARS AND MALE ADULT, 50 YEARS)

Age (years)	Radionuclides							
	^{14}C	^{45}Ca	^{90}Sr	^{22}Na	^{18}F	^{90}Sr+^{90}Y	^{32}P	^{90}Y
9	0.633	0.783	0.972	0.982	0.997	1.041	1.046	1.045
50	0.614	0.762	0.945	0.955	0.971	1.020	1.025	1.025

values of v$\bar{D}_S/D_B$ are given in Table IV for the femoral cortex at the ages 9 and 50 years, which are fairly typical of cortical bone generally. The difference between the dose factors for the two ages is not very great but, because the cavities in cortical bone are much smaller than in trabecular bone, the dose factors are considerably higher, especially at low β-particle energies. It should be noted, however, that there is some evidence to suggest that surface tissues within cortical bone are less sensitive with respect to the development of osteogenic sarcoma than trabecular surfaces (Spiers, *et al.*, 1977).

DISCUSSION

The data given in Table II and Figs. 1 and 2 enable the absorbed dose rates to (1) haemopoietic marrow and (2) endosteal tissues near trabecular surfaces to be calculated from the equation:

$$\text{Absorbed dose to tissue} = D_B \times \text{mean skeletal dose factor} \quad . \quad . \quad . \quad (2)$$

where D_B is given by

$$D_B = 51.2 f C \bar{E}_\beta \quad \text{rad } d^{-1} \quad . \quad . \quad . \quad (3)$$

if f is the fraction of disintegrations in which β-particles of mean energy $\bar{E}_\beta$ MeV are emitted and C is the activity of the skeleton in μCig^{-1}, or by

$$D_B = f C \bar{E}_\beta \quad \text{Gy s}^{-1} \quad . \quad . \quad . \quad . \quad (4)$$

if C is in Bq kg^{-1} and $\bar{E}_\beta$ is in joules.

In the case of the adult, the mass of the mineralized skeleton can be taken formally as 5 kg (ICRP, 1976) and the activity is the retained skeletal activity as determined from metabolic data. For children it is important that appropriate mass and retention data be used in calculating D_B.

Dose rates to tissues near surfaces within cortical bone can be determined similarly from the data in Table IV.

Dose rates to marrow and to trabecular surface tissues for infants of one year or less can be obtained approximately from the data plotted in Figs. 4 and 5, although there must be some reservations as to accuracy because of the extrapolations involved.

For the purpose of dosimetry related to the whole skeleton, multiple bone specimens were available only for three male subjects. Data were obtained, however, for the third lumbar vertebrae from a limited number of both male and female subjects. Where comparisons could be made, for example in the age range 39 to 64 years, the mean path lengths through the trabeculae and marrow cavities of three female vertebrae were somewhat less, on average, than those of seven male subjects. The differences, however, were not significant and the resulting average dose factors for the two sexes did not, in this case, differ by more than ±5%. Moreover, the biological standard deviations in the structural parameters of a particular bone in a given age group have been shown to be of the order of 10% (Beddoe *et al.*, 1976). It seems reasonable, therefore, to use the results given in this paper for β-particle dosimetry in both sexes.

All the calculations are based on the assumption that the bone-seeking radionuclides are uniformly distributed throughout the volume of the mineralized skeleton. Non-uniform distribution will not greatly affect the mean absorbed dose to bone marrow, particularly at high β-particle energies, but will be more serious in respect of the dose near bone surfaces.

If the radionuclide is deposited on bone surfaces, however, the dosimetry is very different from that of the volume-seeker and the dose factors are generally much greater. This may well have clinical significance because some radionuclides may spend an appreciable time on bone surfaces before being finally distributed throughout the bone volume. Absorbed dose factors have therefore been calculated for the case of the surface-seeking radionuclides (Spiers *et al.*, 1978) and the derived mean skeletal dose factors for these will be reported in Part II.

ACKNOWLEDGMENT

This work was carried out with the support of the Medical Research Council.

REFERENCES

BEDDOE, A. H., 1977. Measurements of the microscopic structure of cortical bone. *Physics in Medicine and Biology*, *22*, 298–208.

BEDDOE, A. H., DARLEY, P. J., and SPIERS, F. W., 1976. Measurements of trabecular bone structure in man. *Physics in Medicine and Biology*, *21*, 589–607.

CUSTER, R. P., 1949. In *An atlas of the blood and bone marrow*, p. 30 (W. B. Saunders Co., Philadelphia, Pa., U.S.A.).

ELLIS, R. E., 1961. The distribution of active bone marrow in the adult. *Physics in Medicine and Biology*, *5*, 255–258.

International Commission on Radiological Protection, 1968. A Review of the radiosensitivity of the tissues in Bone, pp. 1–4, *ICRP Publication No. 11* (Pergamon Press, Oxford).

International Commission on Radiological Protection, 1976. Reference Man: Anatomical, Physiological and Metabolic Characteristics, *ICRP Publication No. 23* (Pergamon Press, Oxford).

International Commission on Radiological Protection, 1977. Recommendations. *ICRP Publication No.* 26, p. 10. (Pergamon Press, Oxford).

MARSHALL, J. H., GROER, P. G., and SCHLENKER, R. A., 1974. Dose to endosteal cells and relative distribution factors for radium-224 and plutonium-239 compared with radium-226. *Proceedings of the Alta Conference* (in press).

MECHANIC, N., 1926. Studies of the weight of bone marrow in man. *Zeitschrift für die Gest. Anatomy 79*, 58–99.

SPIERS, F. W., BEDDOE, A. H., KING, S. D., HAYTER, C. J., SMITH, A. H., BURKINSHAW, L., and ROBERTS, B. E., 1976. The absorbed dose to bone marrow in the treatment of polycythaemia by ^{32}P. *British Journal of Radiology*, *49*, 133–140.

SPIERS, F. W., KING, S. D., and BEDDOE, A. H., 1977. Measurements of endosteal surface areas in human long bones: relationship to sites of occurrence of osteosarcoma. *British Journal of Radiology*, *50*, 769–776.

SPIERS, F. W., WHITWELL, J. R., and BEDDOE, A. H., 1978. Calculated dose factors for the radiosensitive tissues in bone irradiated by surface-deposited radionuclides. *Physics in Medicine and Biology*, *23*, 481–494.

VAUGHAN, Janet M., 1973. In *The Effects of Irradiation on the Skeleton*, pp. 40–41 (Clarendon Press, Oxford).

WHITWELL, J. R., 1973. Theoretical investigations of energy loss by ionizing particles in bone, pp. 135–140 (Ph.D. Thesis, University of Leeds).

WHITWELL, J. R., and SPIERS, F. W., 1976. Calculated beta-ray dose factors for trabecular bone. *Physics in Medicine and Biology*, *21*, 16–38.

Book reviews

Abdominal Grey Scale Ultrasonography. Edited by B. B. Goldberg, pp. 372, Illus., 1977 (Sussex, John Wiley & Sons Ltd.), £21·00.

This book represents another in the rapidly increasing texts on grey scale ultrasound. The editor is an acknowledged authority on the subject but I find his book does not come up to my expectations.

The general structure is good with valuable accounts of the physics of grey scale and an excellent chapter on sectional anatomy with some fine colour reproductions of body slices. This chapter could have been longer with advantage. The editor has also invested a great deal of effort in standardizing the image orientation and labelling but, in common with most other texts on this subject, his book suffers from very poor grey scale images. In addition to this the chapter on liver diagnosis was particularly disappointing with poor technique, especially for transverse scans, and failure to display the posterior portion of the liver. Almost all the focal lesions shown in this section are massive and give the reader little idea of the capability of ultrasound to detect much smaller structures.

The other chapters are rather better, though I cannot see why the section on anatomy should be sandwiched between two separate chapters on vessel imaging.

It would have been helpful if one were given some indication of the likely failure rate for ultrasound examinations of the gall bladder, though this chapter is otherwise good with a useful section on the comparison of ultrasonography with other imaging techniques.

The poor image quality unfortunately degrades the otherwise good chapters on renal and retroperitoneal examination and one must hope that Dr. Goldberg will be preparing a second edition with much improved images.

On balance the book can be recommended to those who are involved in non-obstetric abdominal scanning though it should perhaps be used in conjunction with one of the atlases of grey scale images which are now becoming available.

H. B. MEIRE.

Pediatric Oncologic Radiology. Edited by B. R. Parker and R. A. Castellino, pp. xvi+451 illus., 1977 (U.S.A., C. V. Mosby, St. Louis; distributed in UK by Henry Kimpton, London) £31·60.

The incidence of malignant tumours in children is low so most radiologists, unless working in a few large centres, will not see many such cases. The aim of the editors is to provide in a single volume the information which a team concerned with oncology would require to make a rational choice of available techniques of diagnosis.

Part I concerns special procedures with chapters on angiography, neuroradiology, lymphography, nuclear medicine and echography. Part II deals with lymphoreticular malignancies with chapters on leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma and histocytosis X. The third part consists of chapters on Wilm's tumour, neuroblastoma and other adrenal neoplasms, and primary liver tumours, while the final part IV is a miscellany of primary central nervous system and primary bone tumours and rhabdomyosarcoma.

The authors are a distinguished group and their individual contributions deal, not only with diagnostic technique but also with pathology, staging, clinical features, prognosis and treatment. A generous selection of references is included at the end of each chapter and the quality of the illustrations is good.

Although complications of therapy are noted in several chapters, a chapter devoted to unwanted side effects of drugs and irradiation would have been a useful addition. The editors noted themselves that the level of experience of computed body scanning was not great at the time of writing and it will be interesting to see what differences this mode of investigation will make to the second edition of this book which will almost certainly be justified.

The authors stress the need for co-operative management in diagnosis and therapy and this book should appeal to pediatricians as well as being a useful source book for radiodiagnosticians.

D. SHAW.

1978, *British Journal of Radiology*, *51*, 628–630

Technical note

Ultrasonic measurement of renal inclination; its importance in measurement of renal length

By P. Farrant, D.C.R.M.U., and H. B. Meire, F.R.C.R.

Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex

(*Received December, 1977*)

In many X-ray departments the renal bipolar lengths are routinely measured on intravenous urogram films. Whether or not a magnification factor is taken into account to allow for the distance of the kidneys from the film, it is generally assumed that the kidneys lie parallel to the film. Routine ultrasound examinations of the liver frequently show the right kidney (Taylor and Hill 1975), and we have noted that the angle of inclination of the right kidney is not constant from patient to patient. We have therefore performed a retrospective study of 100 patients whose livers had been examined by ultrasound. The renal angle was measured, correlated with age and sex and assessed to determine its influence on X-ray measurements of renal length.

Materials and Method

All patients referred to our hospital with a primary lesion that metastasizes to the liver undergo a routine ultrasound examination of the liver every three months.

Using a Nuclear Enterprises Diasonograph 4200, scans are performed longitudinally and transversely in the supine position, on suspended inspiration. A single pass of the transducer is used where possible, cuts being taken at 1 cm intervals to cover the whole

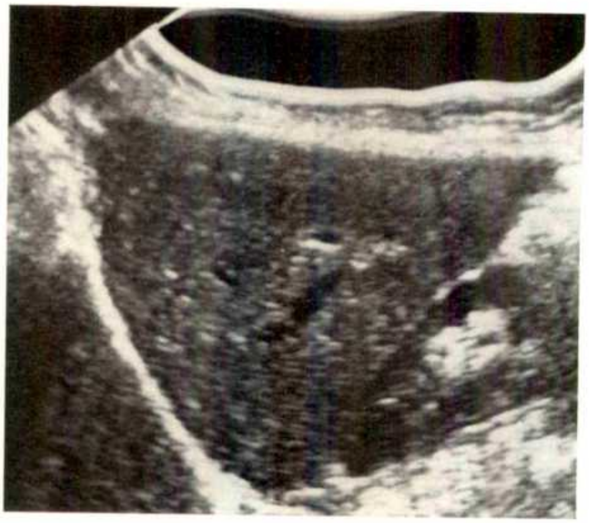


Fig. 2.
A moderately large angle of renal inclination (50 deg.).

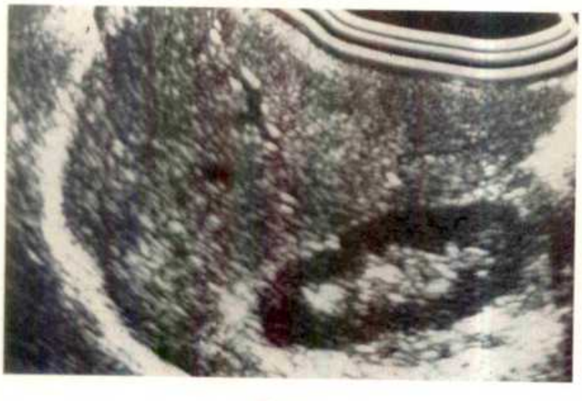


Fig. 1.
A small angle of renal inclination (20 deg.).

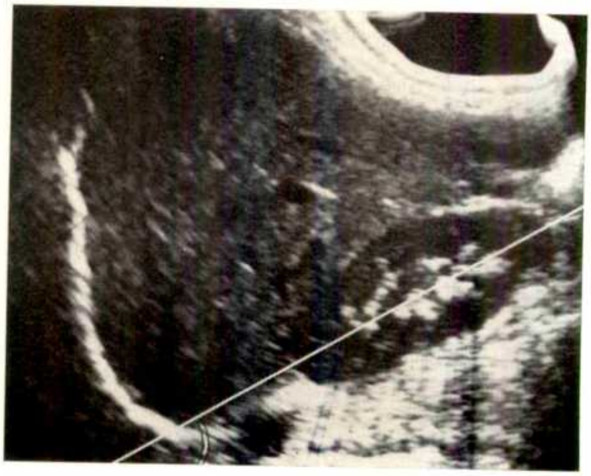


Fig. 3.
Technique for measurement of renal inclination.

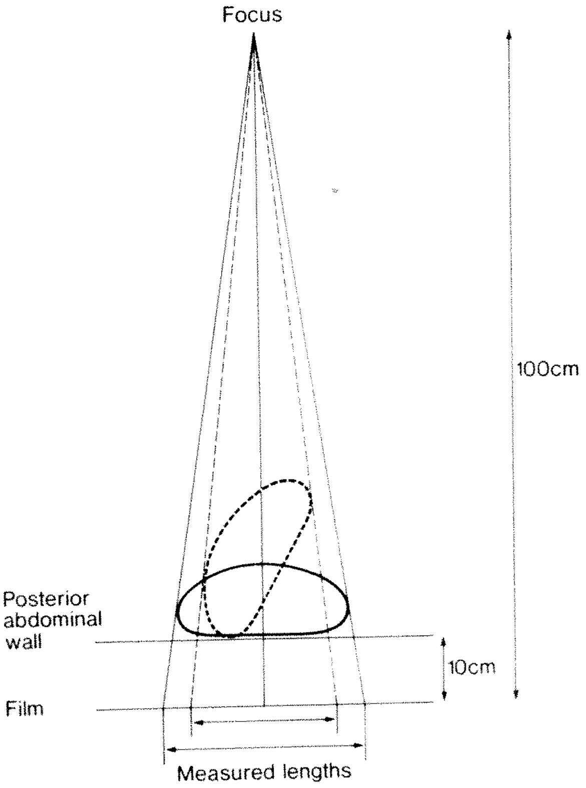


FIG. 4.

Technique for measurement of influence of renal inclination on radiographic renal length.

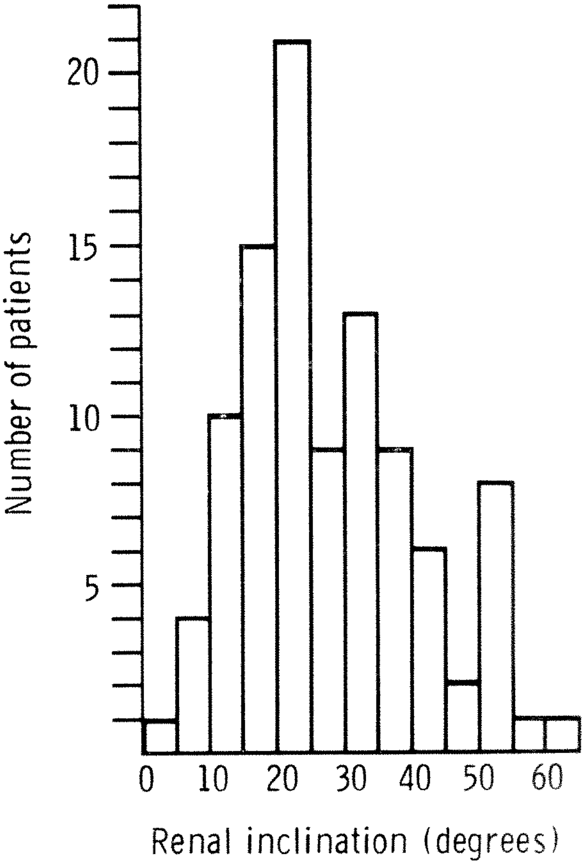


FIG. 5.

Distribution of renal inclinations in 100 patients.

volume of the liver. Each scan is permanently recorded on 70 mm film.

The films were reviewed to identify 100 adult patients in whom the right kidney was sufficiently well seen for measurement of its angle to be made (Figs. 1 and 2). The liver size was judged to be normal in all patients.

The angle of the right kidney was measured by drawing the long axis of the kidney on each film, and the angle of this line with the horizontal was measured (Fig. 3). We confirmed that the films were recorded in a plane parallel to the horizontal, by recording the transducer output signal when the transducer was moved along the surface of the patients' examination trolley. This signal was consistently parallel to the top and bottom margins of the 70 mm films. We also confirmed that the renal angle did not change by more than 5 deg. during respiration.

The influence of the angle of the right kidney on measurement of renal length was assessed by a geometrical model. We assumed a focal film distance of 100 cm and a distance of 10 cm from the film to the posterior abdominal wall. An image of a kidney such as those in Figs. 1–3 was cut out from a photographic print, angled through 5 deg. increments, and the apparent length on the "film" was measured (Fig. 4). We assumed that the upper pole of the kidney lies against the posterior abdominal wall at all angulations (see dotted image in Fig. 4).

RESULTS

The angle of inclination in the 100 patients varied from 5 to 64 deg.; the distribution is seen in Fig. 5.

We had originally thought that the renal angle might correlate with the patient's age and sex, but computer analysis of our data showed no evidence of correlation with age. The mean angle for males was 26.4 deg (S.D. 9.29 deg.) and for females 28.8 deg. (S.D. 13.49 deg.), thus suggesting that there was no significant correlation with sex.

As can be seen from Fig. 4 the renal lengths measured on radiographs vary according to the angle of the kidney to the horizontal. The influence of the angle on percentage error is shown in Fig. 6.

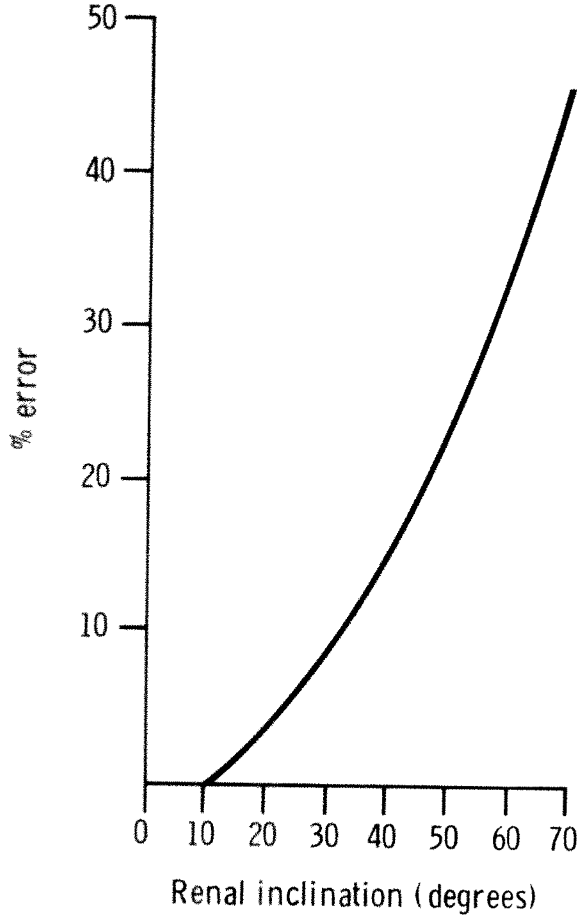


FIG. 6.
Influence of renal inclination on percentage error in measurement of renal length.

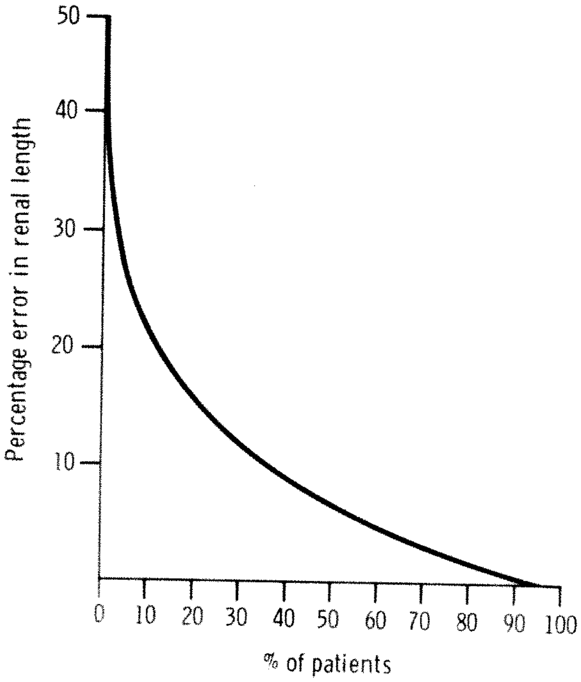


FIG. 7.
Distribution of calculated measurement errors in 100 patients.

If the angle is less than 10 deg. there will be no distortion of renal length, other than by magnification. If the kidney lies at an angle greater than 10 deg. there will be a slight decrease in its apparent length, whereas at angles greater than 30 deg. the measurement obtained would have an error of over 10%. In our patient with an angle of 64 deg. the error in measurement of length would be 40%.

The results were further analysed to determine the distribution of percentage error in measurement of renal length in our patients. This is shown in Fig. 7. It can be seen that only 5% of patients have no error, half of all patients have an error of more than 6%, whilst one in five have an error of greater than 16%.

DISCUSSION

We have shown that in a group of 100 patients with no evidence of hepatic or renal disease, there is a wide variation in the angle which the right kidney makes with the horizontal plane when the patient is supine. Whilst this is unlikely to be of any significance in most patients, we have shown that if renal angles vary similarly in patients having intravenous urograms, significant errors in measurement of renal length may result.

These errors probably contribute to the comparatively wide range of normal renal lengths which are generally used for reference when making measurements from an IVU film. Since all errors represent underestimates of the correct length, the mean values for radiographic renal lengths are probably too small.

In a significant minority of patients the influence of the renal angle on its length measurement will be sufficient to cause an incorrect diagnosis of an abnormally small kidney.

ACKNOWLEDGMENT

We gratefully acknowledge the contribution to this project by Dr. Pauline Lui, visiting registrar to the department.

REFERENCE

TAYLOR, K. J. W., and HILL, C. R., 1975. Scanning techniques in grey-scale ultrasonography. *British Journal of Radiology*, *48*, 918–920.

1978, *British Journal of Radiology*, *51*, 631–632

Case reports

Solitary non-parasitic hepatic cyst presenting with jaundice

By R. J. Machell, M.A., M.B., M.R.C.P., and R. Y. Calne, F.R.S., F.R.C.S., M.S.

Departments of Medical Gastroenterology and Surgery, Addenbrooke's Hospital, Cambridge

(*Received December 1977*)

A case of solitary non-parasitic cyst of the liver, presenting with recurrent obstructive jaundice, is described in a 67-year-old woman.

Solitary non-parasitic hepatic cysts are uncommon and frequently asymptomatic. When symptoms are present they are usually related to abdominal distension with non-specific upper abdominal discomfort. Jaundice has only been described in a few cases.

This report describes a case of solitary non-parasitic hepatic cyst presenting with obstructive jaundice.

CASE REPORT

A 67-year-old woman who first presented with obstructive jaundice in December 1975. Jaundice persisted and laparotomy was performed at another hospital in March 1976. The findings were of an extremely large single cystic lesion replacing the majority of the left lobe of the liver. The right lobe of the liver also looked abnormal. The cyst was opened and a large quantity of thick green bile was removed. No communication between the cyst and the biliary tree could be demonstrated radiologically. The cyst was anastomosed to the front of the gallbladder and a wedge biopsy was taken from the right lobe of the liver, the histology from which showed only a marked cellular infiltration of the portal tracts, with no evidence of bile stasis.

She initially progressed well post-operatively and the jaundice gradually faded. In June 1976, however, there was a recurrence of painless jaundice, accompanied by pruritis, pale stools, dark urine, anorexia and weight loss of one stone. She was referred to Addenbrooke's Hospital for further management.

Physical examination revealed marked jaundice without overt signs of chronic liver disease. The liver extended 3 cm below the right costal margin but there was no splenomegaly nor palpable abdominal mass. Liver function tests showed a total bilirubin 220 μmol/l (normal range 2–14), alkaline phosphatase 400 U/l (normal range 30–92), with a normal SGPT and slightly low plasma albumin. A liver scan showed a large well defined filling defect in the interlobar region of the liver (Fig. 1). Retrograde cholangiography demonstrated a normal calibre common bile duct with a complete blockage in the common hepatic duct proximal to the cystic

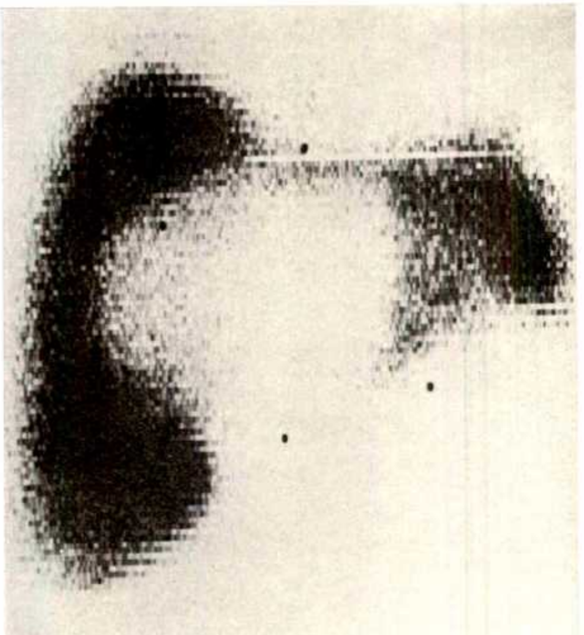


FIG. 1.

^{99}Tc^{m} sulphur colloid liver scan showing a large solitary interlobar filling defect.

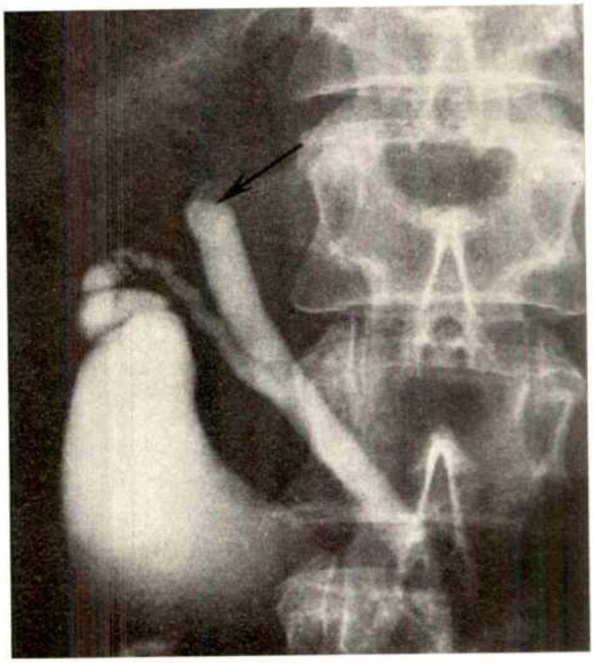


FIG. 2.

Retrograde cholangiogram showing the gallbladder, common bile duct and demonstrating complete blockage of the common hepatic duct.

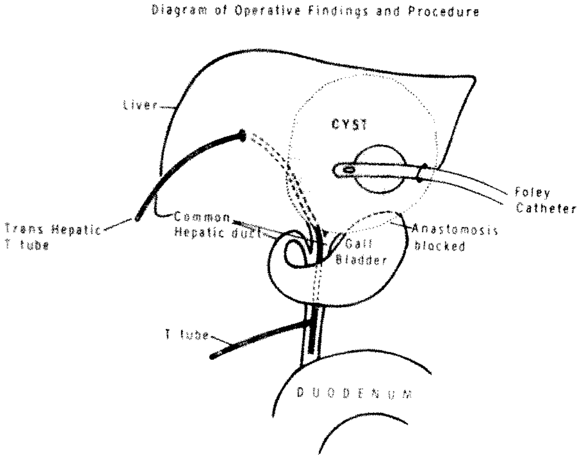


FIG. 3.

Diagram of operative findings and procedure.

duct (Fig. 2). The gallbladder was outlined but there was no passage of contrast from the gallbladder into the cyst, demonstrating blockage of the anastomosis.

It was concluded that this had led to the increased size of the cyst, producing a recurrence of obstructive jaundice. A second laparotomy was performed on 9.7.76 and again a large solitary cyst was found in the left lobe of the liver compressing the common hepatic duct (Fig. 3). The anastomosis between the cyst and gallbladder was noted to be blocked. The common bile duct was opened and a Ryle's tube was passed through the common bile duct, right hepatic duct and out through the right lobe of the liver to the skin. The distal end of this was attached to the long limb of a T tube. One of the short limbs was brought out through the incision in the common bile duct and the other inserted into the distal common bile duct. A large Foley catheter was then inserted into the front of the cyst which deflated and the catheter was brought out through the abdominal incision and left *in situ*. A biopsy was repeated from the right lobe of the liver and the histological appearances were of long standing large duct obstruction with biliary fibrosis. Biopsies from the cyst wall showed inflamed oedematous connective tissue without an epithelial covering. The patient made an uneventful post-operative recovery, with complete resolution of jaundice and return of liver function tests to normal. In October 1976 the Foley catheter draining the cyst was removed and in April 1977 a T tube cholangiogram showed no evidence of biliary obstruction and the T tube was therefore removed.

She has subsequently remained well without recurrence of jaundice.

DISCUSSION

Solitary non-parasitic cysts of the liver are encountered infrequently. They may be true cysts with epithelial lining or false cysts lined by fibrous tissue. They have been classified by Henson *et al.*, (1956) into congenital and acquired varieties. They are more frequent in the age range 40–60, commonest in women and are located most often in the right lobe of the liver.

They are usually asymptomatic. In a review of 82 cases of solitary non-parasitic hepatic cyst at the Mayo Clinic, collected over a 17 year period, Sanfelippo *et al.* (1974), found only 15 patients had symptoms. The remainder were incidental findings at operation for other conditions. In addition liver cysts may be a chance finding at autopsy (De Bakey and Jordan, 1972). When present the commonest symptoms are abdominal fullness and upper abdominal discomfort and the outstanding clinical findings are of an abdominal mass or hepatomegaly (Jones *et al.*, 1974).

Jaundice is an uncommon complication (Hallenbeck and Fricke, 1950) and when it occurs it is usually of the obstructive type, as in our case, caused by extrinsic pressure of the cyst on the extrahepatic biliary tree (Jones *et al.*, 1974).

Occasionally surgical intervention is necessitated by acute complications such as torsion of the cyst (Sood and Watson, 1974), haemorrhage into the cyst, or rupture into the peritoneal cavity (Sanfelippo *et al.*, 1974).

In this case hepatic scintiscanning was most useful in demonstrating the recurrence of the cyst. Ultrasonography has also been described as a valuable technique for the detection of liver cysts and the distinction from solid hepatic tumours. Its application in a case of solitary non-parasitic liver cyst presenting with jaundice was recently reported by Sautman *et al.* (1977). Retrograde cholangiography was also helpful in this case in demonstrating blockage of the anastomosis created at the first operation between the cyst and the gallbladder, which had presumably led to the re-accumulation of the cyst.

REFERENCES

DE BAKEY, M. E., and JORDAN, G. L., JNR. 1972. Cysts in the liver. 3rd edn. Edited by L. Schiff (J. B. Lippincott, Philadelphia). *Diseases of the Liver*, 870–874.

HALLENBECK, G. A., and FRICKE, R. W., 1950. Traumatic bile cysts of the liver: report on two cases. *Mayo Clinic Proceedings*, *25*, 648–651.

HENSON, S. W., JNR., GRAY, H. K., and DOCKERTY, M. B., 1956. Benign tumours of the liver, solitary cysts. *Surgery in Gynaecology and Obstetrics*, *103*, 607–612.

JONES, W. L., MOUNTAIN, J. C., and WARREN, K. W. 1974. Symptomatic non-parasitic cysts of the liver. *British Journal of Surgery*, *61*, 118–123.

SANFELIPPO, P. M., BEAHRS, O. H., and WEILAND, L. H., 1974. Cystic disease of the liver. *Annals of Surgery*, *179*, 922–925.

SAUTMAN, F. W., THIJSH, G., VAN DER VEEN, E. A., DEN OTTER, G., and BLOCK, P., 1977. Intermittent jaundice: a rare complication of a solitary non-parasitic liver cyst. *Gastroenterolgy*, *72*, 325–328.

SOOD, S. C., and WATSON, A., 1974. Solitary cyst of the liver presenting as an abdominal emergency. *Postgraduate Medical Journal*, *50*, 48–50.

1978, *British Journal of Radiology*, *51*, 633–635

Case reports

Anterior vascular indentation of the oesophagus

By W. R. Castaneda-Zuniga, M.D.,* K. Amplatz, M.D.*

Department of Radiology, University of Minnesota Hospitals, 420 Delaware Street S.E., Minneapolis, Minnesota 55455

and J. E. Edwards, M.D.†

Department of Pathology, United Hospitals—Miller Division, St. Paul, Minnesota

(*Received August, 1978 and in revised form January, 1978*)

A case of anterior indentation of the oesophagus by a collateral systemic artery to the lung in pulmonary atresia is described. Such indentation by an anterior structure is usually considered diagnostic of an aberrant left pulmonary artery.

CASE REPORT

An 18-year-old male with a diagnosis of "pseudotruncus arteriosus" was admitted to the University of Minnesota Hospitals and underwent open heart surgery. A thoracic roentgenogram at the time of admission revealed cardiomegaly, a prominent ascending aorta with a left aortic arch and increased pulmonary vascularity (Fig. 1A). On the lateral thoracic roentgenogram a soft tissue mass was seen above the level of the carina displacing the oesophagus posteriorly and the trachea anteriorly (Fig. 1B). A thoracic aortogram revealed the presence of a large systemic artery arising from the right side of a high aortic arch and crossing the mediastinum from left to right between the oesophagus and trachea to supply the right upper lobe (Fig. 2). At the time of surgery the ventricular septal defect was closed. An

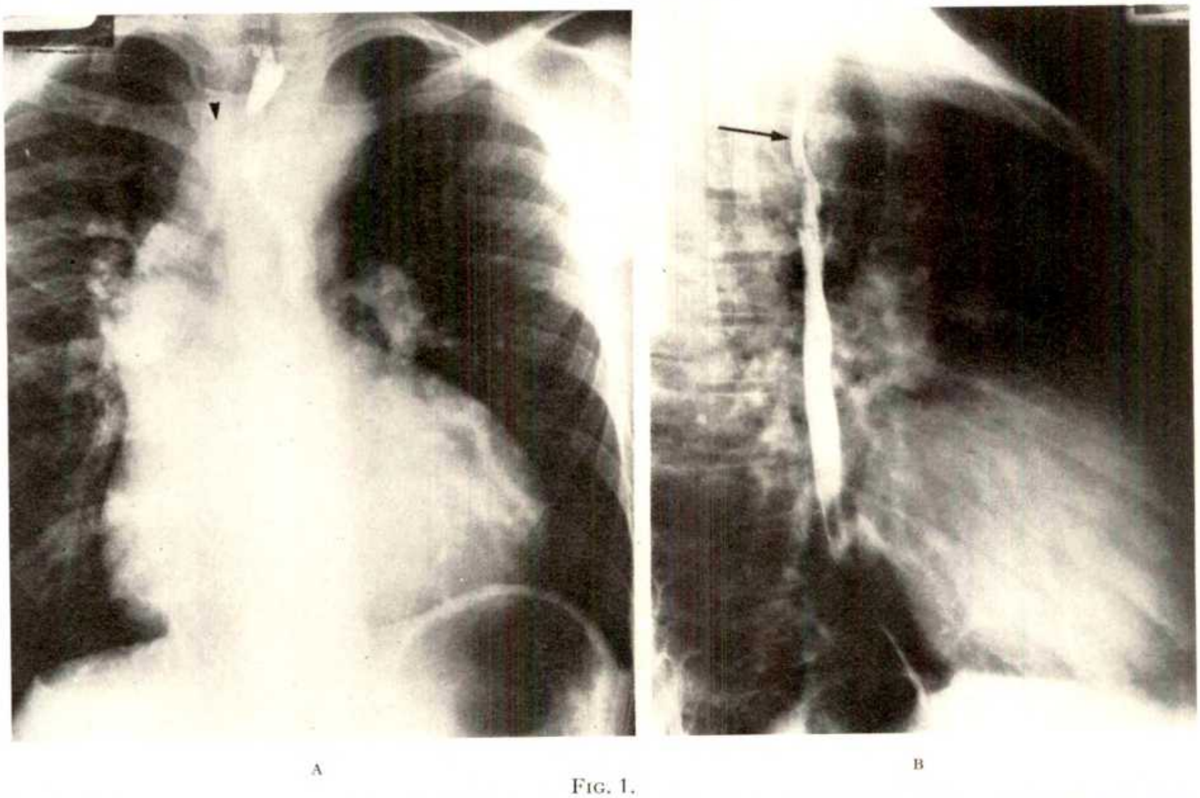
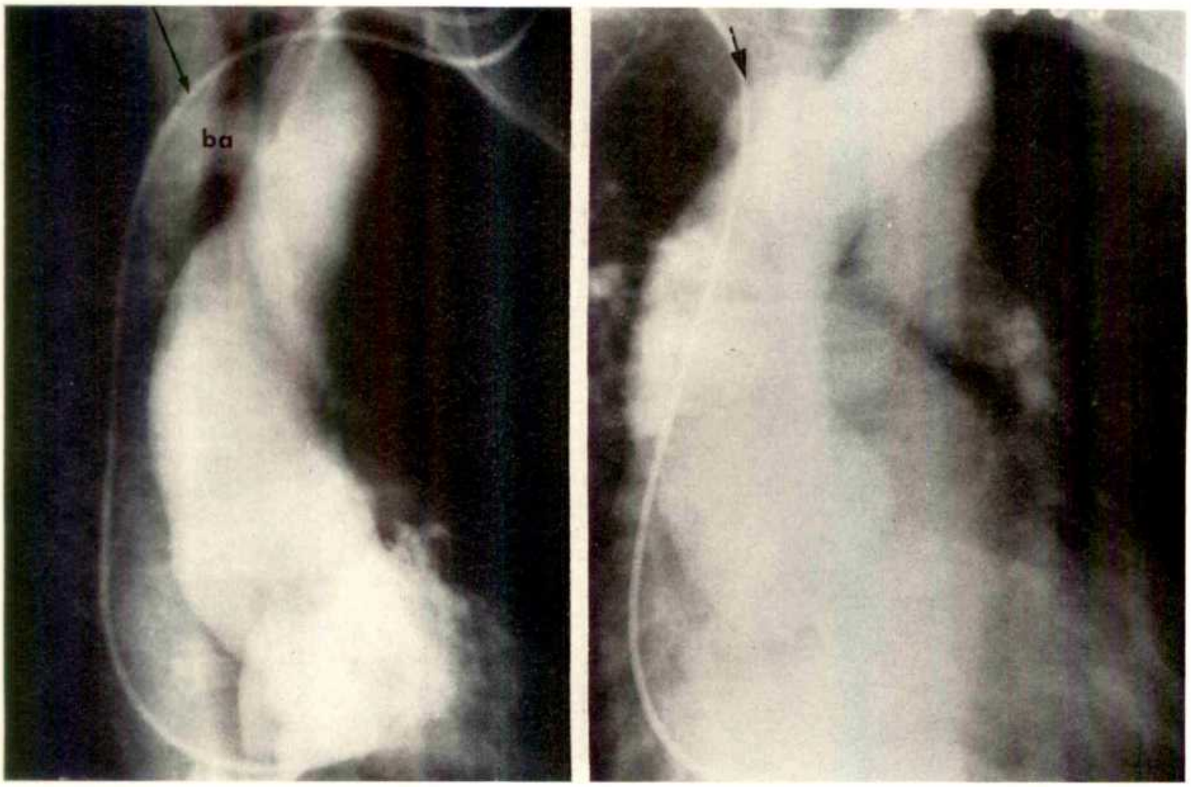


FIG. 1.

(A) Chest roentgenogram reveals unequal vascularity with decreased vascular markings in the left lung field. Cardiomegaly with concave pulmonary segment and a wide ascending aorta with a left arch. A double density is projected to the right of the trachea (arrowhead).

(B) The lateral thoracic roentgenogram reveals a soft tissue mass above the level of the carina displacing the oesophagus posteriorly and the trachea anteriorly (arrow).

This work was supported in part by US Public Health Service grants HL-5853 from the National Heart and Lung Institute and 2 PO1 HE 06314* and Public Health Service Research Grant 5 RO1 HLO5794 and Research Training Grant 5 TO1 HLO5570 from the National Heart and Lung Institute†.



A

B

Fig. 2.

(A) A right ventriculogram reveals the presence of pulmonary atresia with a ventricular septal defect and an overriding aorta. A large vessel (ba) is seen arising from the aortic arch and crossing from left to right to supply the right lung (arrow).

(B) An aortogram reveals the presence of a ductus-like artery supply both the right and left pulmonary arteries. A large artery arises from the aortic arch and crosses the mediastinum from left to right between the oesophagus and trachea to supply the right upper lobe (arrow).

aortic homograft was placed from the right ventricle to the pulmonary artery, and a patent ductus arteriosus was ligated.

After surgery he improved gradually and remained relatively asymptomatic for a period of time. He was readmitted for evaluation of possible aortic valvar or homograft valvar insufficiency. At time of catheterization a small residual ventricular septal defect with a 25 to 35% left-to-right shunt, pulmonary hypertension, and both aortic valve and aortic homgraft valvar insufficiency were found. It was decided that he should undergo surgery to correct the insufficiency of both of the semilunar valves, as well as close the residual ventricular septal defect. The postoperative course was very complicated, and he died despite all the measures attempted.

The postmortem examination confirmed the diagnosis of pulmonary atresia, surgically closed ventricular septal defect, right ventricular outflow—pulmonary artery conduit, surgically ligated ductus arteriosus, and a large systemic artery arising from the right side of the aortic arch between the origins of the left carotid and left subclavian arteries and crossing the mediastinum from left to right between the oesophagus and trachea to supply the right upper lobe (Fig. 3)

DISCUSSION

Anterior indentation of the oesophagus and posterior compression of the trachea above the level of the carina have been described in cases of aberrant left pulmonary artery (also referred to as pulmonary sling or origin of the left pulmonary artery from the right pulmonary artery (Clarkson, 1967; Felson, 1973; Kale *et al.*, 1970). The indentation of the oesophagus is seen above the carina, since the aberrant artery crosses over the right bronchus and then passes between the trachea and oesophagus to enter the hilum of the left lung. The indentation in our case was slightly higher than usually seen with aberrent left pulmonary artery. Another rare vascular cause of anterior indentation of the oesophagus is a normally connecting pulmonary vein although seen at a much lower level (Felson, 1973).

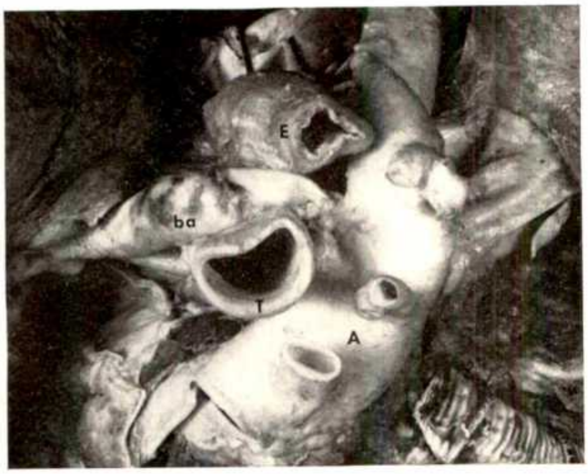


FIG. 3A.

A photograph of the specimen from above reveals the presence of a large systemic artery (ba) arising from the right of the aortic arch (A) and crossing the mediastinum from left to right between the oesophagus (E) and trachea (T) to supply the right lung.

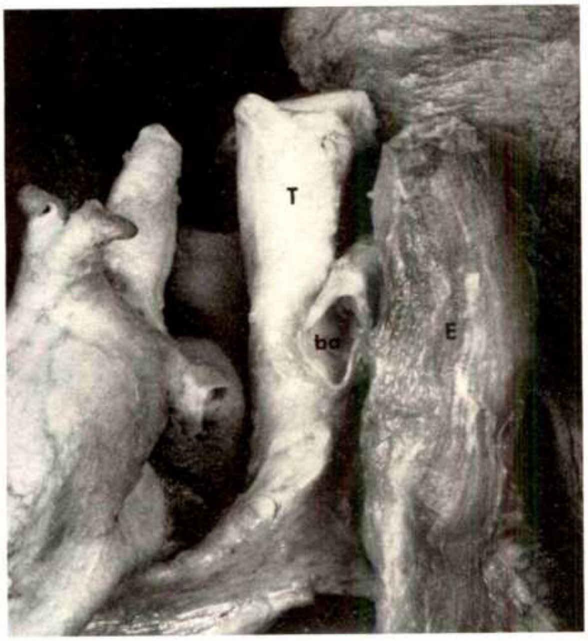


FIG. 3B.

A lateral view of the specimen shows the systemic artery as it crosses between the trachea and oesophagus.

More commonly, non-vascular structures such as lymph nodes, cysts or tumours, may produce posterolateral displacement of the oesophagus (Felson, 1973; Fleischner and Sachsse, 1963).

Characteristically in pathologic specimens of pulmonary atresia, wide systemic collateral arteries to the lung on the side opposite to that of the descending aorta pass behind the oesophagus. Those collaterals to the lung on the same side as the descending aorta do not have a close relationship with the oesophagus (Edwards, personal communication).

In the early English literature, and still in some textbooks, anterior indentation of the oesophagus was described by an aberrant brachiocephalic artery (Gross and Neuhauser, 1951; Holzapfel (quoted by Goldloom 1922), but it is now certain that aberrant brachiocephalic arteries always cross behind the oesophagus resulting in posterior indentation (Edwards, 1953).

SUMMARY AND CONCLUSION

Although anterior indentation of the oesophagus by a vascular structure is usually considered diagnostic of an aberrant left pulmonary artery, a case is reported where such an indentation was caused by systemic collateral artery in pulmonary atresia crossing from left to right between the trachea and oesophagus. The artery produced a visible density on plain roentgenograms. Anterior vascular indentation of the oesophagus is still most likely due to an aberrant left pulmonary artery, but the possibility of a systemic collateral artery should be kept in mind.

REFERENCES

CLARKSON, P. M., 1967. Aberrant left pulmonary artery. *American Journal of Diseases of Children, 113*, 373–377.

EDWARDS, J. E. Personal Communication.

1953. Malformations of the aortic arch system manifested as "vascular rings". *Laboratory Investigation 2*, 56–75.

FELSON, B., 1973. *Chest Roentgenology*, pp. 208 (W. B. Saunders Co., Philadelphia).

FLEISCHNER, F. G. and SACHSSE, E., 1963. Retrotracheal lymphadenopathy in bronchial carcinoma, revealed by the barium filled oesophagus. *American Journal of Roentgenology, 90*, 792–798.

GROSS, R. E. and NEUHAUSER, E. B. D., 1951. Compression of the trachea or oesophagus by vascular anomalies. *Pediatrics*, 7, 69–83.

HOLZAPFEL, G., quoted by GOLDBLOOM, A. A., 1922. Anomalous right subclavian artery and its possible clinical significances. *Surgery, Gynecology, and Obstetrics, 34*, 378–384.

KALE, M. K., RAFERTY, R. E., and CASTON, R. W., 1970. Aberrant left pulmonary artery presenting as a mediastinal mass: report of a case in an adult. *Archives of Internal Medicine, 125*, 121–125.

1978, *British Journal of Radiology*, *51*, 636–637

Short communications

Cytotoxicity and radiosensitization in mouse and man

By Juliana Denekamp

Gray Laboratory, Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

(*Received January, 1978*)

Drugs which specifically sensitize hypoxic cells to radiation, *e.g.* the nitroimidazoles, have been shown to be effective on bacterial and mammalian cells *in vitro*, and on rodent and human cells *in vivo* (for a comprehensive summary see the Proceedings of the 8th L. H. Gray Conference, Cambridge, 1977). These compounds can substitute for oxygen as a radiosensitizer.

Since their introduction as radiosensitizers it has been discovered that these compounds also have a specific cytotoxic effect on hypoxic cells in the absence of radiation (Sutherland, 1974; Begg *et al.*, 1974; Denekamp and Harris, 1975; Foster and Willson, 1973, 1976; Sheldon and Hill, 1977; Stratford and Adams, 1977). Prolonged exposure to the drug under hypoxic conditions is necessary before significant cell killing occurs (*e.g.* several hours in 0.5–1.0 mM misonidazole at 37°C; Stratford and Adams, 1977). It has been postulated that this cytotoxicity may play an important role in man where the half-life of the drug is long (10–14 hours; Flockhart *et al.*, 1977), but it is difficult to demonstrate in the mouse because the half-life is only 1–1.5 hours. Nevertheless a significant though small cytotoxic effect has been demonstrated in half the types of tumour tested in mice by giving large doses of the drugs misonidazole *after* irradiation, thereby avoiding direct radiosensitization. The results are summarized in Table I.

One of the first methods of testing the sensitizers clinically involved patients with multiple subcutaneous metastatic nodules. In each patient some of the nodules were irradiated without drug, and other nodules were irradiated three to five hours after drug administration. Using this approach Thomlinson *et al.* (1976) demonstrated a difference in the growth delay of three groups of metastatic nodules, indicating that sensitization by a dose modifying factor of 1.2 had been achieved with a single dose of 4.0 g misonidazole. However, in such a study the drug was given systematically and *all* tumour cells were exposed to its cytotoxic action, although only those irradiated shortly after administration were exposed to its radiosensitizing action. Any difference in response between the two groups, therefore, represents the effect of radiosensitization over and above the cytotoxic effect, as illustrated in Fig. 1. The DMF of 1.2 was therefore an underestimate of the total benefit of misonidazole. This has not previously been appreciated. The extent to which it is underestimated is unknown, but will depend upon the importance of cytotoxicity in man.

Several clinical trials are in progress to determine the therapeutic potential of metronidazole and misonidazole (see Proceedings of Gray Conference 1978). In most of these trials separate groups of patients are being treated with fractionated radiotherapy either without the drug, or with the drug given several hours before irradiation to achieve the maximum tumour concentration at irradiation. These trials include treatments with relatively few large radiation doses, each with a high drug dose (*e.g.* Urtasun *et al.*, 1975, 1976, 1977; Bleehen; Dische; Kogelnick, Phillips; Urtasun; in Proceedings of Gray Conference 1978), and also schedules using very many small daily fractions with low daily drug doses which may possibly maximise the cytotoxic effect (Dische *et al.* in Proceedings of Gray Conference 1978). Urtasun *et al.* (1976) have also proposed a third arm to their trial in which the drug would be administered *after* irradiation in order to test for any direct cytotoxicity.

It is clear that clinical trials in which two groups of patients are compared, one with and one without the sensitizer, will be a measure of the total benefit and will include *both* radiosensitization and cytotoxicity. However, studies of multiple metastases in the same patient will only measure the additional radiosensitization since all the tumour nodules will be exposed to the cytotoxic action of the drugs.

TABLE I

CYTOTOXICITY AND RADIOSENSITIZATION: SUMMARY OF MOUSE TUMOURS.
ENHANCEMENT RATIOS IF 1 MG/G/ MISONIDAZOLE IS GIVEN BEFORE OR AFTER IRRADIATION

After	Before	Tumour	Reference	After	Before	Tumour	Reference
1.2	2.3	C3H Ca	Brown, 1975	0.9	2.1	MT/1MT	Sheldon and Hill, 1977
1.3	2.2	Sq Ca D	Hill and Fowler, 1977	1.0	2.1	Fib/T	McNally (unpub.)
1.3	2.1	Ca NT	Denekamp and Harris, 1975	1.0	1.8	B Sa 2	Denekamp (unpub.)
1.1	1.9	Fibrosa	Stewart (unpub..)	1.0	1.8	C3H Ca	Sheldon *et al.*, 1974
1.4	1.9	Rhod Ca	Denekamp (unpub.)	1.0	1.7	Disc Ca	Hirst (unpub.)
1.3	1.7	Sa F	Begg (unpub.)	1.0	1.7	FF Sa 1	Hirst (unpub.)
1.2	1.6	FFSa2	Hirst (unpub.)	1.0	1.5	Sa F	Begg (unpub.)
			7/14 Some cytotoxicity				7/14 No cytotoxicity

Drug given before irradiation demonstrates both cytotoxicity and radiosensitization
Drug given after irradiation demonstrates only cytotoxicity

1978, *British Journal of Radiology*, *51*, 637–639 AUGUST 1978

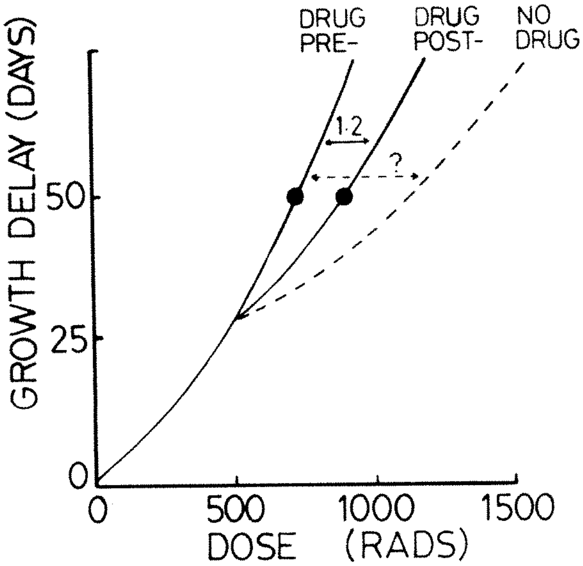


FIG. 1.

Schematic representation of the growth delay induced in subcutaneous nodules from human Ca cervix (data from Thomlinson *et al.*, 1976). Nodules treated with 800 rad 3–4 hours after ingestion of 4 g misonidazole showed the same growth delay as tumours treated with 960 rad before the drug was administered. The dose modifying factor of 1.2 represents additional sensitization since all hypoxic cells were exposed to the systemically administered drug.

The total combined radiosentitising and cytotoxic effect of the drug is unknown, but must be greater than 1.2.

REFERENCES

BEGG, A. C., SHELDON, P. W., and FOSTER, J. L., 1974. Demonstration of hypoxic cell radiosensitization in solid tumours by metronidazole. *British Journal of Radiology*, *47*, 399–404.

BROWN, J. M., 1975. Selective radiosensitization of the hypoxic cells of mouse tumours with the nitroimidazoles metronidazole and Ro-07-0582. *Radiation Research*, *64*, 633–674.

DENEKAMP, J., and HARRIS, S. R., 1975. Tests of two electron affinic radiosensitizers *in vivo* using regrowth of an experimental carcinoma. *Radiation Research*, *61*, 191–203.

FLOCKHART, I. R., LARGE, P., TROUP, D., MALCOLM, S. L., and MARTEN, T. R., 1977. Pharmacokinetic and metabolic studies of the dypoxic cell radiosensitizer misonidazole. *Xenobiotica*, *8*, 97–105.

FOSTER, J. L., and WILLSON, R. L., 1973. Radiosensitization of anoxic cells by metronidazole. (Correspondence.) *British Journal of Radiology*, *46*, 234–235.

1976. Metronidazole (Flagyl) in cancer radiotherapy. *Chemotherapy*, *7*, 215–222.

HILL, S. A., and FOWLER, J. F., 1977. Radiosensitizing and cytocidal effects on hypoxic cells of Ro-07-0582, and repair of X-ray injury, in an experimental mouse tumour. *British Journal of Cancer*, *35*, 461–469.

Proceedings of the 8th L. H. Gray Conference on Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy, 1978, Editors G. E. Adams and P. Wardman. *British Journal of Cancer*, *37*, (in press.).

SHELDON, P. W., FOSTER, J. L., and FOWLER, J. F., 1974. Radiosensitization of C3H mouse mammary tumours by a 2-nitroimidazole drug. *British Journal of Cancer*, *30*, 560–565.

SHELDON, P. W. and HILL, S. A., 1977. Further investigations of the effects of the hypoxic-cell radiosensitizer, Ro-07-0582, on local control of a mouse tumour. *British Journal of Cancer*, *36*, 198–205.

STRATFORD, I. J., and ADAMS, G. E., 1977. The effect of hyperthermia on the differential cytotoxicity of the hypoxic cell radiosensitizer Ro-07-0582 on mammalian cells *in vitro*. *British Journal of Cancer*, *35*, 307–313.

SUTHERLAND, R. M., 1974. Selective chemotherapy of noncycling cells in an *in vitro* tumor model. *Cancer Research*, *34*, 3501–3503.

THOMLINSON, R. H., DISCHE, S., GRAY, A. J., and ERRINGTON, L. J., 1976. Clinical testing of the radiosensitizer Ro-07-0582. III. Response of tumours. *Clinical Radiology*, *27*, 167–174.

URTASUN, R. C., CHAPMAN, J. D., BAND, P., RABIN, H. R., FRYER, C. G., and STURMWIND, J., 1975. Phase 1 study of high-dose metronidazole: a specific *in vivo* and *in vitro* radiosensitizer of hypoxic cells. *Radiology*, *117*, 129–133.

URTASUN, R. C., BAND, P., CHAPMAN, J. D., WILSON, A. F., MARYNOWSKI, B., and STARREVELD, E., 1976. Metronidazole as a radiosensitizer: correspondence. *New England Journal of Medicine*, *295*, 901–902.

URTASUN, R. C., BAND, P., CHAPMAN, J. D., RABIN, H. R., WILSON, A. F., and FRYER, C. G., 1977. Clinical phase one study of the hypoxic cell radiosensitizer Ro-07-0582, a 2-nitroimidazole derivative. *Radiology*, *122*, 801–804.

Pitfalls in the use of *in vitro* survival curves for the determination of tumour cell survival with fractionated doses

By L. Zeitz, Ph.D. and J. M. McDonald, Ph.D.

Biophysics Laboratory, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021

(*Received August, 1977 and in revised form March, 1978*)

Ellis (1974) and Habermalz and Fischer (1976) have suggested that "high-individual-dose-fractionation schedules" would be expected to give better results in the therapy of malignant melanoma based on the large shoulders exhibited by the survival curves of some malignant melanoma cell lines (Dewey, 1971; Barranco *et al.*, 1971). It has already been pointed out that there is no consensus regarding a large shoulder for malignant melanoma cells (Zeitz and Silagi, 1977).

This communication shows that the original estimate by Ellis (1974) of a great improvement in sterilization of malignant melanoma tumours through the use of a small number of large doses (7 × 620 rad) as opposed to a large number of small doses (31 × 200 rad) was greatly exaggerated because the expression applied, $S = 1 - (1 - e^{-D/D_0})^n$, gave a poor fit to the data (Dewey, 1971) used in making his prediction of survival probability. Although not discussed here, it can be shown that the same conclusion holds for the improvement estimated by Habermalz and Fischer (1976) based on the survival data reported by Barranco *et al.* (1971) for cell lines isolated from human solid malignant tumours. These conclusions are not unexpected if one considers the observations of Chapman *et al.* (1975), Elkind (1975) and others who have pointed out the "critical importance" of the initial shape of the survival curve in applying single-cell survival curves for estimation of the degree of sterilization of tumour cells with radiotherapy.

The survival data of Dewey (1971) for oxic Harding-Passey mouse melanoma cells irradiated with 250 kV X rays are reproduced in Fig. 1 with assumed errors of ±10% in survival and ±2% in dose. These estimated errors were not given by Dewey (1971) and are based on our own experience (Zeitz *et al.*, 1975; Zeitz *et al.*, 1977) and that of others. Also given in Fig. 1 are: (1) a curve (long dashes) based on the multitarget expression, $S = 1 - (1 - e^{-D/D_0})^n$, $n = 25$, $D_0 = 85$ as used by Ellis (1974), (2) a non-linear least square fit (LSF) as in Bevington (1969) to the multi-target model, the solid curve, (3) an LSF to the multitarget model with initial slope (Bender and Gooch, 1962), $S = e^{D/D_1}[1 - (1 - e^{-D/D_0})^n]$, the dot-dash curve, and (4) the short dash curve for the LSF with the linear-quadratic expression (Sinclair, 1965), $S = e^{-(\alpha D + \beta D^2)}$. The multitarget with initial slope and the linear-quadratic expressions were chosen because (a) the evident non-zero slope at low dose for the Dewey data suggested that these functions would probably give better fits than the multitarget expression, (b) they have been shown in many cases to give good fits to survival curve data measured in tissue culture (Sinclair, 1965; Chapman *et al.*, 1975), and (c) there is some theoretical justification for the multitarget model with initial slope from Bender and Gooch (1962), and for the linear-quadratic expression from the dual radiation action theory of Kellerer and Rossi (1972). Chi-square analyses (Bevington, 1969) show that the multitarget model with initial slope gives the best fit and the multitarget model the poorest as expected from a study of Fig. 1.

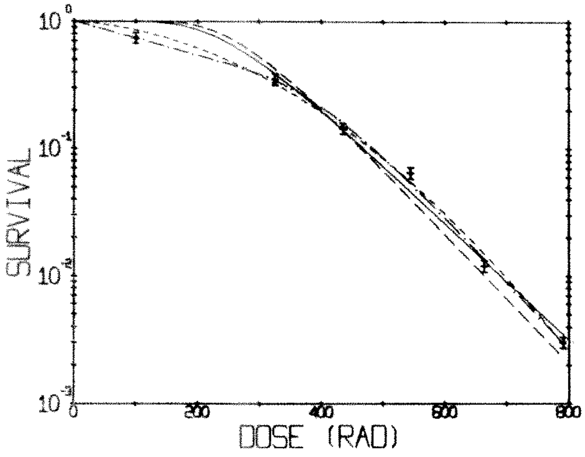


FIG. 1.

The radiation survival data of Dewey (1971) for Harding-Passey cells in culture after 250 kV X irradiation and various fits to this data. A non-linear least square fit with the multitarget equation (———), with the multitarget model with a non-zero initial slope (— · —), with the linear-quadratic expression (---), and a curve (— — —) based on the multitarget equation with $n = 25$, $D_0 = 85$ rad as used by Ellis (1974).

Table I gives the survival to be expected with different fractionation schedules suggested by Ellis (1974). The survival after an individual dose was determined on the basis of the four "fits" given above. In calculating the survival probabilities after fractionated doses the assumptions, similar to those made by others (Suit *et al.*, 1967), are that all treated tumour cells were aerobic with the same curve shape as exhibited by the particular tissue-culture survival curve, that there was full repair of sublethal damage and no proliferation between treatments, and that there was no change in the distribution of cells in the cell cycle in the course of treatment.

The calculated survival probability for the treatment with 31 fractions at 200 rad with the best fits given in Table I (i.e., for the initial slope multitarget and the linear-quadratic models) are, respectively, 1×10^7 and 2×10^5 times less than that determined by Ellis (1974) with the multitarget expression. As would be expected, the predicted survival probabilities approach each other more closely for the various "fits" with large individual doses of 620 rad or more.

It is very likely that the shape for the *in vivo* curves in the low dose region differ from the *in vitro* curves by amounts equal to the differences between the various curves of Fig. 1. If this proves to be the case, then the possible errors involved in estimating *in vivo* survival probabilities with multiple low dose fractions from *in vitro* survival curves could be so large as to make an estimate of little or no value, even disregarding the well known complications in extrapolating the *in vivo* situation already enumerated.

TABLE I

CELL SURVIVAL PROBABILITY FROM DATA OF DEWEY (1971)

Fraction schedules considered by Ellis (1974)	31 × 200 rad	7 × 620 rad	4 × 960 rad	3 × 1200 rad
As determined by Ellis (1974) with multitarget expression. $n = 25$ and $D_0 = 85$ rad	7.5×10^{-2}	3.9×10^{-13}	9.4×10^{-15}	6.3×10^{-15}
LSF to multitarget expression $n = 15$ and $D_0 = 94$ rad	6.7×10^{-3}	1.4×10^{-12}	9.2×10^{-14}	7.9×10^{-14}
LSF to linear-quadratic expression $\alpha = 7.4 \times 10^{-4}$ rad^{-1}, $\beta = 8.4 \times 10^{-6}$ rad^{-2}	3.0×10^{-7}	6.2×10^{-12}	2.1×10^{-15}	1.2×10^{-17}
LSF to multitarget expression with initial non-zero slope $D_1 = 327$ rad, $D_0 = 108$ rad, $n = 53$	5.7×10^{-9}	3.2×10^{-12}	1.9×10^{-14}	7.0×10^{-15}

ACKNOWLEDGMENTS

We thank Drs. J. H. Kim and J. S. Laughlin for their helpful comments. This work was supported in part by NCI Grant No. CA 08748-12 and ERDA Contract ERDA Contract EE-77-S-02-4268.

REFERENCES

BARRANCO, S. C., ROMSDAHL, M. M., and HUMPHREY, R. M., 1971. The radiation response of human malignant melanoma cells grown *in vitro*. *Cancer Research*, *31*, 830–833.

BENDER, M. A., and GOOCH, P. C., 1962. The kinetics of X-ray survival of mammalian cells. *International Journal of Radiation Biology*, *5*, 133–145.

BEVINGTON, P. R., 1969. Least square fit to an arbitrary function. *Data Reduction and Error Analysis for the Physical Sciences*, pp. 204–246.

CHAPMAN, J. D., GILLESPIE, C. J., REUVERS, A. P., and Dugle, D. L., 1975. The inactivation of Chinese hamster cells by X rays: the effects of chemical modifiers on single- and double-events. *Radiation Research*, *64*, 365–375.

Dewey, D. L., 1971. The radiosensitivity of melanoma cells in culture. *British Journal of Radiology*, *44*, 816–817.

ELKIND, M. M., 1975. Cell survival after low doses of radiation: theoretical and clinical implications, *Proceedings of the Sixth L. H. Gray Conference*, September 1974 (pp. 376–388).

ELLIS, F., 1974. The NSD concept and radioresistant tumours. *British Journal of Radiology*, *47*, 909.

HABERMALZ, H. J., and FISCHER, J. J., 1976. Radiation therapy of malignant melanoma. Experience with high individual treatment doses. *Cancer*, *38*, 2258–2262.

KELLERER, A. M., and ROSSI, H. H., 1972. The theory of dual radiation action. *Current Topics in Radiation Research Quarterly*, *8*, 85–158.

SINCLAIR, W. K., 1965. The shape of radiation survival curves of mammalian cells cultured *in vitro*. In *Biophysical Aspects of Radiation Quality*, International Atomic Energy Agency, Technical Report Series No. 58, pp. 21–43.

SUIT, H., REIMUT, W., and LINDLEY, R., 1967. Analysis of tumour-recurrence times. *Radiology*, *88*, 311–321.

ZEITZ, L., CANADA, T. R., DJORDJEVIC, B., DYMBORT, G., FREEMAN, R., MCDONALD, J. C., O'NEIL, J., and LAUGHLIN, J. S., 1975. A biological determination of the variation of fast-neutron field quality with depth, OER and RBE. *Radiation Research*, *63*, 211–225.

ZEITZ, L., KIM, S. H., and KIM, J. H., 1977. Determination of relative biological effectiveness (RBE) of soft x-rays. *Radiation Research*, *70*, 552–563.

ZEITZ, L., and SILAGI, S., 1977. Radiosensitivity of melanoma cells in culture: implications for radiotherapy of malignant melanoma. *British Journal of Radiology*, *50*, 604–606.

Book review

The Handling, Storage, Use and Disposal of Unsealed Radionuclides in Hospitals and Medical Research Establishments. Annals of the ICRP, Vol. 1, No. 2, 1977, pp. vi+46 1977 (*ICRP Publication 25*), £4·50.

The reports and recommendations of the ICRP are now published in this new review journal of which there will be four issues each year. Each issue will deal with a specific radiation protection topic including such subjects as "developing an index of harm", "protection in uranium mines" and "biological effects of inhaled radionuclides" (a more complete list is to be found in this issue). This present publication replaces the previous recommendations of those set out in ICRP publication No. 5 and is the result of the efforts of a task group set up in 1971. The task group's material was edited by Committee three (external exposures) and Committee four (application of recommendations) of the ICRP. Unlike publication five it does not deal with sealed sources; recommendations concerning these are to be found in publication 15. Although it is primarily directed towards national authorities, it will certainly be of value to hospital and research institutes where unsealed sources are used for diagnosis, therapy or research.

Although only a relatively slim volume, it deals with every aspect of protection concerned with unsealed sources and has a generous reference list, including not only previous ICRP publications but also those of the IAEA, WHO and material taken from the UK "Code of Practice for Medical and Dental Use". There are a number of useful tables in the document. These include: radionuclides frequently used in medicine (with exposure rate constants and annual limits of intake), radiation doses to patients in some types of examinations with radionuclides (organ, gonad and whole body), facilities required in relation to the category of hazard and a list of radiation monitoring equipment.

There is a brief mention of the use of radionuclides in research and the particular problem of authorization of the administration of radionuclides to normals or volunteers. Another section deals with the more recent problems that arise from the increasing use of generators, stressing the necessity to check for the presence of significant quantities of parent material in the eluate.

The whole text gives one the impression that the task group have made every effort to bring the subject matter up to date and have considered every aspect of the modern uses of radionuclides. The only section that I think could be criticized is the data given in Table 8. These data give the maximum time that ward staff may spend (at 1m distance) with a patient containing, for example, 150 mCi of iodine 131. It is difficult to see how the actual times were derived and it might give the impression that they are acceptable times, which they are not.

Finally, it gave this reviewer great pleasure to read "the curriculum for medical students should include at least the foundation that is necessary for an understanding of the basic aspects of radiation protection with regard to the exercise of good clinical judgment". T. H. E. BRYANT.

1978, *British Journal of Radiology*, *51*, 640–643

Proceedings of The British Institute of Radiology

In vivo and *in vitro* radioisotope investigations of diseases involving the endocrine organs

Abstracts of papers read at a meeting held on February 16, 1977 at The British Institute of Radiology (Reid-Knox Hall), Institute House, 32 Welbeck Street, London W1M 7PG.

Thyroid function after radioiodine treatment of thyrotoxicosis, by A. D. Toft and W. J. Irvine.
Improved data handling for thyroid health care, by P. R. Edwards, G. Malan, R. P. Ekins, E. R. Carson, K. E. Britton and L. Finkelstein.
Use of thyroid function test data in clinical practice, by K. E. Britton, P. R. Edwards, E. R. Carson, R. P. Ekins, G. Malan and L. Finkelstein.
^{131}I iodo-cholesterol: the present position, by K. E. Britton.
^{75}Se-sitosterol, a new reagent for suprarenal scintigraphy, by P. H. Cox, P. Ph. H. L. Otto and A. P. M. van der Veek.
The development of selenium-75 labelled cholesterol analogues for adrenal scintigraphy, by J. A. Peacegood, R. D. Pickett, and A. L. M. Riley.
Clinical evaluation of a new ^{75}Se-labelled agent for adrenal scintigraphy, by R. Montz, J. Hagemann and W. Mischke.
The radioimmunoassay precision profile: a guide to radioimmunoassay design and optimal counter usage, by R. P. Ekins (*no abstract received*).

THYROID FUNCTION AFTER RADIOIODINE TREATMENT OF THYROTOXICOSIS

By A. D. Toft and W. J. Irvine

Endocrine Unit, Royal Infirmary and University Department of Therapeutics, Edinburgh

It is now apparent that the pituitary thyrotroph is suppressed by the prolonged high levels of circulating thyroid hormones in thyrotoxicosis, analogous to the suppression of the pituitary-adrenal axis in patients maintained on pharmacological doses of corticosteroids. Following the reduction of serum total thyroxine (T4) and serum total tri-iodothyronine (T3) levels to normal or even low values after radioiodine treatment of thyrotoxicosis, there is a delay of four to eight weeks before normal thyrotroph function is regained. The association of low serum total T4 and T3 but normal serum thyrotrophin (TSH) levels is not infrequently observed in the early weeks of follow-up in patients ultimately developing clinical hypothyroidism within six months of iodine-131 therapy for thyrotoxicosis. The measurement of serum total T4 is therefore of more value than the serum TSH in predicting the early onset of clinical hypothyroidism after iodine-131 therapy.

On the other hand, in the long-term follow-up of patients treated with iodine-131 for thyrotoxicosis, the measurement of the serum TSH level can be used to predict those patients at increased risk of hypothyroidism. Thus, in 1972, 58% of patients euthyroid after iodine-131 therapy for thyrotoxicosis between 1954–66 had a raised serum TSH level (7.4 mU/l) and 42% a normal TSH level. A group of 69 of the euthyroid patients with a raised serum TSH level (25.0±2.0 mU/l) in 1972 was re-examined annually until 1976. There was no apparent change in the mean serum TSH level between 1972–76 in the patients remaining euthyroid, but overt hypothyroidism developed in 11 patients during the 4.5 years of study. In contrast, none of a group of 61 patients, euthyroid with a normal serum TSH level (4.0±0.2 mU/l) in 1972, developed overt hypothyroidism between 1972–76, although raised serum TSH levels were recorded in 14 patients during the study. The follow-up of patients with normal serum TSH levels after iodine-131 treatment for thyrotoxicosis need not be so frequent as that of similarly treated euthyroid patients with raised serum TSH levels in whom overt hypothyroidism develops at the rate of 2–5% per year.

The mean serum total T4 in the euthyroid patients with a raised serum TSH level was significantly lower, but still in the normal range, than that in the euthyroid patients with a normal serum TSH level. The mean serum total T3 was also lower in the euthyroid patients with raised serum TSH levels, but only significantly lower in 1975 and not in 1976. It is not yet known whether suboptimal thyroid hormone levels and a raised serum TSH level is detrimental to the patient in the long-term, although some centres routinely treat such patients with thyroxine.

IMPROVED DATA HANDLING FOR THYROID HEALTH CARE

By P. R. Edwards*, G. Malan†, R. P. Ekins† E. R. Carson*, K. E. Britton‡ and L. Finkelstein*

**Department of Systems Science, City University and* *†Middlesex Hospital, ‡St Bartholomew's Hospital*

A collaborative investigation is being undertaken, applying systems techniques to the selection and interpretation of thyroid hormone assays. Improved patient management and an increased efficiency of assay service operation are sought through the use of a computer-based system to capture and process thyroid patient data routinely supplied by physicians.

The information processing occurring within the assay service and between the service and the physician can be viewed as a data-processing centre separated from its users. On the basis of a systems analysis, improvements have been recommended for improved data processing in the assay service. These improvements are being implemented in a number of stages with at each stage feedback being sought from the users as to their compatability and usefulness within the existing hospital environment. A pilot study is being implemented to examine the acceptability of these recommended changes.

Having established an improved problem-orientated data base, its use for better patient management is being investigated. Statistical models drawn from pattern recognition and control theory as decision aids in the diagnosis and treatment of thyroid disease are being evaluated using preliminary data and will shortly be used with the pilot study data referred to above.

Reprints of these abstracts may be obtained free on application to The Managing Editor, THE BRITISH JOURNAL OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG (01–935 6867).

Throughout, emphasis is placed upon useful aids to clinical decision making, predicting the patient's response to therapy rather than extending or duplicating the physician's role. The advanced theoretical techniques used are of value only if they can be shown to result in improved care for thyroid patients at the Middlesex Hospital.

USE OF THYROID FUNCTION TEST DATA IN CLINICAL PRACTICE

By K. E. Britton‡, P. R. Edwards*, E. R. Carson*, R. P. Ekins†, G. Malan† and L. Finkelstein*

‡*St. Bartholomew's Hospital*, **Systems Science Department, City University and* † *Middlesex Hospital School, London.*

Review of 1500 consecutive request forms for thyroid function tests showed uncertainty in the clinical diagnosis in 47%. Decision aiding ranges were introduced so that the results of a free thyroxine index measurement was divided into five categories: definitely hyperthyroid, borderline hyperthyroid on which samples a total T_3 was automatically performed, definitely euthyroid, borderline hypothyroid on which samples a TSH measurement was automatically performed, and definitely hypothyroid. Depending on clinical and therapy data, these simple procedures were overruled or augmented (Britton *et al.*, 1975). Using this simple strategy, diagnostic uncertainty was reduced to under 2% This work was undertaken by hand and formed a pilot study for developing data handling systems appropriate to the best use of a small computer to facilitate the working of the strategy.

REFERENCE

BRITTON, K. E., QUINN, V., BROWN, B. L., and EKINS, R. P., 1975. A strategy for thyroid function tests. *British Medical Journal 3*, 350–352.

^{131}I IODO-CHOLESTEROL: THE PRESENT POSITION

By K. E. Britton

Department of Radioisotopes and Nuclear Medicine,
St Bartholomew's Hospital, West Smithfield,
London EC1A 7BE

Experience with adrenal scanning in 60 patients is reviewed. The technique consists of: day 1, injecting 1.5 mCi ^{131}I iodo-cholesterol intravenously; day 3, injecting 0.5 mCi ^{99}Tc^{m} sulphur colloid plus 1 mCi ^{99}Tc^{m} DMSA intravenously followed by a fast kidney scan to localize the adrenals and then a slow adrenal + liver, spleen, kidney scan over a very small area using double isotope technique and computer analysis; and on day 6 repeating the adrenal scan. For days 0–6, 120 mg KI is given orally daily.

Forty-one patients with suspected Conn's syndrome showed about 88% correct prediction of normals and of the side of the tumours or hyperplasia. Seventeen patients with Cushing's syndrome, scanning showed about 87% correct prediction of the side of the tumour or hyperplasia. Depending on diagnostic criteria, 11 to 13 out of 14 diagnoses were confirmed at operation in these 58 patients. The laterization of one phaeochromocytoma and the diagnosis of hyperplasia in one patient with congenital adrenal hyperplasia were established.

^{131}I Iodo-cholesterol is a useful adrenal scanning agent but its cost and the absorbed radiation dose are considerable deterrents to its routine use. ^{123}I iodo-cholesterol should be developed.

^{75}SE-SITOSTEROL, A NEW REAGENT FOR SUPRARENAL SCINTIGRAPHY

By P. H. Cox,

Rotterdamsch Radio-Therapeutisch Instituut, Department of Nuclear Medicine, Groene Hilledijk 301, Rotterdam-Z, The Netherlands

P. Ph. H. L. Otto and
A. P. M. van der Veek

Centraal Laboratorium T.N.O., Postbox 217, Delft, The Netherlands

Sitosterol has been used in clinical practice for its effect on cholesterol metabolism and is therefore a potential reagent for adrenol scintigraphy. It is possible to label sitosterol with ^{75}Se and the resultant compound is stable and appears to be a promising reagent for the study of the adrenals.

In pilot studies this substance has proved to have a number of advantages over labelled cholesterols, being more stable and more rapidly eliminated from the body. Studies of organ distribution suggest that scintigrams could be made earlier than with cholesterol and a progressive uptake in the adrenals introduces the possibility of evaluating the functional state of the organs.

THE DEVELOPMENT OF SELENIUM-75 LABELLED CHOLESTEROL ANALOGUES FOR ADRENAL SCINTIGRAPHY

By J. A. Peacegood, R. D. Pickett and A. L. M. Riley

The Radiochemical Centre, Amersham, Bucks

The development and assessment in animals of 19-methylselenocholesterol-^{75}Se and 6-β-methylselenomethyl-19-norcholest-5(10)-en-3β-ol-^{75}Se is summarized. The second agent shows particular promise and results of a clinical assessment (R. Montz) are described in a separate paper at this meeting.

CLINICAL EVALUATION OF A NEW ^{75}SE-LABELLED AGENT FOR ADRENAL SCINTIGRAPHY

By R. Montz, J. Hagemann, and W. Mischke (with the technical assistance of G. Lilienthal)

Department of Nuclear Medicine and II. Medical Clinic, University Hospital Hamburg-Eppendorf, W. Germany

There has been general agreement that adrenal scintigraphy with ^{131}I-19-iodocholesterol is of value in localizing adrenal lesions and dysfunctions, especially adrenocortical adenomas. However, the handling of the radiopharmaceutical and the scanning procedure involve a number of problems. These have been discussed only rarely, but the difficulties have been described during announcements of new agents (Kojima *et al.*, 1975; Sarkar *et al.*, 1975; Beierwaltes *et al.*, 1976; Röder *et al.*, 1977) and in descriptions of complicated techniques for subtraction and quantification of the scintigraphic data (Britton *et al.*, 1976; Koral and Sarkar, 1977). The main problems in our experience with 40 patients studied from 1973 to 1976 were: (1) instability of the ^{131}I-labelled agent, not allowing storage for more than a few days and (2) the need for long scanning times (40–60 min) in spite of rather large doses administered (1–2 mCi). The latter was required because of the unfavourable balance between the very slowly increasing ratio of adrenal to background radioactivity and the relatively rapid decay of the ^{131}I-activity.

Recently, a new adrenal scanning agent has been obtained from The Radiochemical Centre, Amersham, Buckinghamshire, U.K.: 6-methyl[^{75}Se] selenomethyl-19-norcholest-5 (10)-en-3β-ol. During a clinical trial, since April 1976 with 52 patients we have found several advantages with this agent. These are summarized in comparison with our own experiences with ^{131}I-19-iodocholesterol, using our technique of quantitative adrenal gamma-camera scintigraphy (Montz *et al.*, 1973), which is essentially the same as published recently by Koral and Sarkar (1977). The advantages found are:

(1) better counting efficiency (by a factor of 1.4) for ^{75}Se versus ^{131}I,
(2) higher uptake by normal adrenal cortex and by hyperfunctioning glands or adenomas,
(3) an enhanced difference between radioactivity in adrenals and background activity (a factor of two) and
(4) excellent stability of the agent (as judged from unaltered scanning results after storage of the material at 4°C for more than three months).

In consequence, a nuclear medicine department may stock this ^{75}Se-labelled norcholesterol for immediate use. Doses of about 200μCi (or 3 μCi/kg body weight) are sufficient to obtain better scintigraphic results, with reasonable scanning times of 15 minutes, within two to six days after tracer injection. The dose of absorbed radiation to the patient is lower than for 1 mCi of the ^{131}I-labelled agent because of the lack of β-radiation and in spite of the longer physical half-life of ^{75}Se of 118.5 days. A disadvantage is that repeated studies are difficult because of the variable persistence of ^{75}Se in the adrenals (mean effective half-life=43 days, range=10–100 days).

The normal range of ^{75}Se-norcholesterol uptake for a single adrenal was 0.15–0.30% of dose ($n=8$ patients without evidence of adrenal disease), similar to the values of 0.23±0.03% (1 s.d.) reported for ^{131}I-6β-iodomethyl-19-norcholesterol (Koral and Sarkar, 1977). In our clinical results there was no overlap between the normal uptake values and those from patients with hypercortisolism ($n=16$) or adrenal hypofunction ($n=14$). Localization of adrenocortical adenomas was correctly predicted in five patients with hypercortisolism, four with hyperaldosteronism and one with androgen excess. One aldosteronoma of 2.5 g could not be detected, the study being done without dexamethasone premedication.

In summary, adrenal scintigraphy with the new ^{75}Se-labelled norcholesterol is easier, quicker and more reliable than it was using ^{131}I-19-iodocholesterol, and the new agent has some technical advantages over ^{131}I-6β-iodomethyl-19-norcholesterol.

REFERENCES

Beierwaltes, W. H., Wieland, D. M., Ice, R. D., Seabold, J. E., Sarkar, S. D., Gill, S. P., and Mosley, S. T., 1976. Localization of radiolabelled enzyme inhibitors in the adrenal gland. *Journal of Nuclear Medicine 17*, 998–1001.

Britton, K. E., Goodwin, T. J., Peart, W. S., and Snell, M. E., 1976. Adrenal aldo-sterone-producing adenoma: use of colonic potential in diagnosis and subtraction scanning technique for localisation. *British Medical Journal, 2*, 11–14.

Kojima, M., Maeda, M., Ogawa, H., Nitta, K., and Ito, T., 1975. New adrenal-scanning agent. *Journal of Nuclear Medicine, 16*, 666–668.

Koral, K. F., and Sarkar, S. D., 1977. An operator-independent method for background subtraction in adrenal uptake measurements: concise communication. *Journal of Nuclear Medicine, 18*, 925–928.

Montz, R., Nowakowski, H., Mischke, W., Höhne, K.-H., and Pfeiffer, G., 1973. Ergebnisse der Nebennieren-Sequenzszintographie mit 131Jod-19-Jodcholesterol. *Radiobiologia-Radiotherapie, 6*, 740–741.

Röder, E., Focken, P. H., Biersack, H. J., and Winkler, C., 1977. Radioiodinated hydroxyphenylethylamine derivatives of digitalis glycosides and their aglucones as scanning agents for adrenal imaging. *IRCS Medical Science, 5*, 542.

Sarkar, S. D., Beierwaltes, W. H., Ice, R. D., Basmadjian, G. P., Hetzel, K. R., Kennedy, W. P., and Mason, M. M., 1975. A new and superior adrenal scanning agent, NP-59. *Journal of Nuclear Medicine 16*, 1038–1042.

Real-time ultrasound

Abstracts of papers presented at the Institute House, 32 Welbeck Street, London W1M 7PG on Thursday, October 20, 1977.*

The contribution of echocardiography, by D. G. Gibson.
Real-time imaging in cardiology, by R. B. Pridie.
Real-time ultrasound in obstetrics, by S. Campbell (*no abstract received*).
Real-time ultrasound in the abdomen, by D. Cosgrove.

THE CONTRIBUTION OF ECHOCARDIOGRAPHY

By D. G. Gibson

Brompton Hospital, London SW3 6HP

Analysis of cardiac function depends on recording information about movement as well as structure. For the former, M-mode echocardiography is the method of choice on account of its repetition frequency of 1000/sec, its ability to localize endocardium, and the versatility of the display on a strip chart recorder. Examples of simple off-line computer methods of analysing mitral valve and left ventricular wall movement are given. For anatomical information a two-dimensional approach is preferable. Of currently available methods, the 90 deg phased array sector-scanner seems most suitable. The potential and limitations of this technique were discussed, illustrated by the output of a prototype EMI machine. Ideally, both methods should be available on a single machine.

REAL-TIME IMAGING IN CARDIOLOGY

By R. B. Pridie

Harefield Hospital, Uxbridge, Middlesex UB9 6JH

The fact that two-dimensional imaging of the heart is in real time is not an advantage. What is required is a permanent record of the movement. This can be achieved either by videotape recording or cine photography of the oscilloscope.

---

*Reprints of these abstracts are available free on application to the Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG, telephone 01–935 6867.

Cine is convenient for most cardiac X-ray departments which will have 35 mm processing equipment for angiocardiography.

Early efforts at cross-sectional imaging of the heart using an R-wave triggered Picker B-scan enabled end systolic and diastolic frames to be recorded. Such echograms were time consuming to make and only possible in patients in sinus rhythm. When the B-scan was linked with a computer, continuous recordings could be made throughout the cardiac cycle with a simultaneous electrocardiogram. The computer then displayed the data as a compound B-scan of all lines recorded in each 10 mm second interval following the R-wave of the ECG. Tolerable images of the contracting ventricle were produced but the variation of the R-R interval which occurs with respiration affects diastole principally and made the diastolic images unrecognizable.

The Vidison was also tried. This is a device in which two transducers rotate at the focus of a parabolic mirror inside an oil-filled rubber bag which is applied to the precordium. Although images of the moving heart can be obtained, the amount of distortion associated with this machine makes accurate measurements impossible.

The linear array of multiple small transducers which are fired sequentially was invented by Nicklaus Bomm and we had the privilege of working with one of the first prototypes. This ingeneous device also had some problems which are largely associated with beam spread and with the side lobes which cause a certain amount of distortion. These are now being overcome in late modifications by focussing the transducers. Steering the beam electronically has now become a practical proposition and in my view probably offers the best hope for high quality two-dimensional echocardiography.

The other method of ultrasonic two-dimensional scanning is the use of the sector scanner. This too is now producing high quality echograms.

REAL-TIME ULTRASOUND IN THE ABDOMEN

By D. Cosgrove

Department of Nuclear Medicine
Royal Marsden Hospital
Downs Road, Sutton, Surrey

For the cardiologist, motion as on the M-mode display has always been the mainstay of echo diagnosis; for him the new real-time technology has offered the possibility of an additional spatial dimension which he is probably not exploiting to the full as yet. In the abdomen, when real time was offered, the reverse question posed itself: what could we do with an added time dimension on top of the familiar two spatial dimensions of the tomograms that are the daily sliced loaf?

As yet I feel we have not made full use of this asset, but life is full of surprises and we have found that it is an extra spatial dimension rather than the temporal one that has come out of these machines. This arises because, for the first time, we can work without the severe restraints imposed by the scanning gantry or frame. This disposed of, the operator is free to choose any plane for his 2D slice which is now generated automatically by the machine, and what is more, to change its angulation and orientation rapidly and precisely so that anatomical structures can be explored, outlines and vessels followed without ever losing the image and so rapidly that the mind receives a 3D view of the anatomy in question. Appreciation of this is best in real life when one senses the orientation of the transducer with the examining hand. It is similar to the use of a conventional B scanner in the slow-scan or search mode, but is much more effective. For this, one does not require very fast frame rates (electronic storage can be used to produce flicker-free images) and a rate of one or two frames a second seems to be ideal.

We observed this effect first when using the longest established of the contact real-time scanners, the ADR (Kretz) which produces a linear scan. This type of scanner is simple in construction (and therefore reliable and relatively cheap) and usefully portable. The image is an acceptable rectangle but it suffers in general abdominal use by requiring a large contact surface—the image width is equal to the contact length. This forces a tiresome compromise between an image of interpretable size and a probe small enough to allow use of the small acoustic windows that are part of the everyday headaches of abdominal scanning.

The Emisonic 4500 phased array system provides a solution to this problem—although there are drawbacks here too. It scans a 90 deg. sector arc from a contact area of about 2.5 cm square and this allows access to anatomical sites that are ordinarily very difficult to scan. Not only is this an advance over the linear array systems, but because it exposes 45 deg. of tissue to either side of the transducer centre line, it offers a substantial improvement in access over the conventional B scanner in scanning awkward sites like the anterior portion of the liver, the left hemidiaphragm, the upper poles of kidneys and the prostate. It also allows one to view around abdominal gas barriers to areas that are obscured to conventional scanners. Unfortunately it is impossible to display the skin line, and the first 1 or 2 cm of subcutaneous tissue are not imaged. This is disorientating and in some situations a heavy penalty since a substantial amount of anatomy occurs here—*e.g.* in children, or in thin adults when the anterior wall of the gall bladder and the whole pancreas may be lost to view. The 90 deg. field is not a great limitation in practice although it makes later interpretation of the images somewhat difficult.

The speed with which one can analyse complex anatomical problems is remarkable, and of course this is closely related to ease of learning—one needs a good knowledge of anatomy, pathology and medicine but little technical expertise is required. This has been a feature of newer developments in ultrasound; the open shutter grey scale technique was difficult to master—the scan converter eased this problem and now real time offers further improvement in ease of use.

We have assessed the time needed to image some critical organs by clocking three experienced observers and comparing times on the phased array and on the B scanner. The targets chosen were the upper poles of the kidneys, the superior mesenteric vessels (an index of the location of the head of the pancreas) and the cystic duct as a marker for bile ducts. In each case the real time machine was quicker, and also remarkable was the much lower rate of failure to image the target.

Since the body is 3D and moves, the ideal imaging system must deal with all of these modalities and the new real time scanners come close to achieving this. At present we prefer the phased array system for ease of access to difficult anatomical areas, and it is excellent for defining gross anatomy and tubular structures—far better than the B scanner. However, the images are still not as good as those obtainable from the best B scanners, so for more subtle problems, for example small liver secondaries, the B scanner is preferred. New techniques in ultrasound have made previously difficult investigations routinely available and this certainly is true of the real time system. The newer developments have also opened new research areas but so far this has not been demonstrated from this group of machines. It seems certain however that we could make more use of the tissue movement displayed.

1978, *British Journal of Radiology*, 51, 644–652

Proceedings of the British Medical Ultrasound Society

Abstracts of papers presented at the ninth annual meeting of the British Medical Ultrasound Society (formerly the British Medical Ultrasonics Group) held on December 7–8, 1977 at the Institution of Electrical Engineers, Savoy Place, London

New developments in dynamic focussing and in computer analysis of M-mode and 2D images, by N. Bom, J. Vogel, F. Hagemeijer and H. Rijsterborgh.
Cardiac imaging with a real-time ultrasonic scanner of a rotating transducer design, by C. R. Bow, W. N. McDicken, T. Anderson, R. E. Scorgie, R. S. Sapru and A. L. Muir.
Selective apical septal hypertrophy in right ventricular volume overload, by J. Gehrke.
Beat to beat variation of aortic valve leaflets' peak velocities in congestive cardiomyopathy and low output in coronary artery disease, by H. H. Schmitz, R. K. Oxenham and K. H. Parker.
Clinical use of distance and amplitude measurements in ophthalmic ultrasonography, by W. Buschmann and D. Linnert.
3-D multiplanar scanning principles, by T. G. Brown.
The ultrasonic signs of fetal death in the first trimester, by G. B. Young.
24 hour studies of fetal respiratory movements (FRMs) and fetal body movements (FBMs) in normal and abnormal pregnancies, by A. B. Roberts, D. Little and S. Campbell.
Ultrasonic scanning in suspected ectopic pregnancy, by Jan Fog Pedersen and Rene Fiege.
A comparison of biparietal measurements using a real time scanner and a conventional scanner equipped with a coded cephalometry system, by A. H. Adam, H. P. Robinson, A. J. Hall and J. E. E. Fleming.
The prediction of birthweight in the breech fetus, by V. Poll.
Ante-natal screening for neural tube defects, by A. D. Christie and W. G. Millar.
A revolution in resolution, by Hylton B. Meire.
The differential diagnosis of jaundice by means of grey-scale ultrasound B-scan, by J. M. G. Chu, D. O. Cosgrove and V. R. McCready.
The use of ultrasound and HIDA in the investigation of jaundice, by A. E. A. Joseph, K. C. Dewbury, D. M. Ackery, N. W. Garvie and P. McGuire.
Studies in cancer treatment with ultrasound, by F. W. Kremkau.
Real-time improvement of lateral and range resolution by optical signal processing, by J. C. Somer.
A comparison of grey scale recording media, by Hylton B. Meire.
Ultrasonic image storage and manipulation by microprocessor, by P. T. Ostro and L. Harrison.
Combining vessel imaging and blood velocity measurement, by P. J. Fish, I. M. Wilson, T. I. H. Brown, B. Deakin and M. Barrett.
A real-time B scan/pulsed Doppler system for fetal breathing and other obstetrical studies, by T. Anderson, W. N. McDicken, R. McHugh, C. R. Bow, K. Boddy, R. Cole, P. Thomson and G. B. Young.
Physiological significance of blood-velocity/time waveforms recorded from normal and disease arteries, using Doppler shift flowmeters, by R. Skidmore and J. P. Woodcock.
Assessment of abnormalities in cardiac output by transcutaneous aortovelography, by L. H. Light.
Attenuation of ultrasound in normal and ischaemically injured myocardium, by J. G. Miller.
The diffraction of ultrasound by human tissues: a clinical tool? by D. Nicholas.
Time analysis of echograms by complex demodulation, by R. Kruizinga and J. M. Thijssen.
Some problems in the characterization of ultrasonic transducers, by J. C. Gore and S. Leeman.
Waveform variations in pulsed ultrasonic beams – a computer study, by F. A. Duck.

NEW DEVELOPMENTS IN DYNANIC FOCUSSING AND IN COMPUTER ANALYSIS OF M-MODE AND 2D IMAGES

By N. Bom, J. Vogel, F. Hagemeijer and H. Rijsterborgh

Thoraxcenter, Erasmus University, and
Interuniversitair Cardiologisch Instituut,
Rotterdam, The Netherlands

In order to improve two-dimensional real time image quality, research was carried out particularly directed towards improvement of lateral resolution in the scanning plane. For the linear array or multiscan method a dynamic focussing technique is presented. With six sequential focus zones and a 51-element transducer employed at 3.12 MHz the resolution can be maintained within 3 mm over 16 cm depth when measured at the —10dB level. (Ligtvoet *et al.*, 1977).

From the M-mode record, data may be obtained with a pencil follower and be used for further calculation by computer. Computer analysis of routine echocardiograms is an ideal tool to enforce a uniform and standardized analysis. With instantaneous display of data and requests on a TV memory the program guides the operator through a prescribed sequence. A standardized analysis program yields information on data such as ventricular inner diameter, septal thickness, mitral valve amplitude etc.

Not only a routine program has been developed but also experimental analysis programs with associated graphics. Here for instance the shortening rate may be shown as function of time during one cardiac cycle. (Vogel *et al.*, 1977)

Much more complicated equipment is necessary if studies are to be carried out on real time recorded two-dimensional images. Most of the effort here is aimed towards automatic pattern recognition, but also various display methods, fusing time and 2D information, may be studied. These studies are carried out in co-operation with the Technical University, Delft.

Both two-dimensional real time imaging and M-mode registration have become routine methods in many cardiac departments. The two methods complement each other, and are often used in conjunction. The paper discusses new developments in both areas.

REFERENCES

LIGTVOET C. M., RIDDER J., LANCÉE C. T., HAGEMEIJER F. and VLETTER W. B. 1977. A dynamically focused multiscan system. *Echocardiology*, pp.313–323. (Martinus Nijhoff, The Hague) ISBM 90.247.2009.5.

VOGEL J. A., VAN ZWIETEN G. and BOM N., 1977. Data processing of time-motion information in echocardiography. *Echocardiology*, 335–347 (Martinus Nijhoff, The Hague).

CARDIAC IMAGING WITH A REAL-TIME ULTRASONIC SCANNER OF A ROTATING TRANSDUCER DESIGN

By C. R. Bow, W. N. McDicken, T. Anderson,

Department of Medical Physics, Royal Infirmary, Edinburgh

R. E. Scorgie, R. S. Sapru and A. L. Muir

Department of Medicine, Royal Infirmary, Edinburgh

A real-time ultrasonic scanner, which utilizes a rotating transducer, has been constructed and applied to study the heart. Features of the instrument are described. Enclosing the transducer in a fluid filled chamber of thin-walled construction makes it particularly suitable for clinical use. The large variable angle field of view is also of value. Results from applications of this scanner in cardiology are presented. Methods of recording high quality real-time B-scan images are discussed. The real-time scanner has proved to be well suited to other areas of study such as obstetrics and general abdominal studies.

SELECTIVE APICAL SEPTAL HYPERTROPHY IN RIGHT VENTRICULAR VOLUME OVERLOAD

By J. Gehrke

Department of Medicine, Division of Cardiovascular Disease (Clinical Cardiology), Royal Postgraduate Medical School, Hammersmith Hospital, London

Real-time B-scan echocardiography has recently demonstrated a characteristic "see-saw" motion of the interventricular septum in patients with right ventricular volume overload. Increasing septal amplitude of motion towards the cardiac apex suggested that left ventricular ejection may mainly be performed by the apical interventricular septum. To support this hypothesis the septum of 20 patients with clinical right ventricular volume overload due to tricuspid regurgitation or pre-tricuspid left to right shunts were examined by M-scan and real-time B-scan echocardiography. Interventricular septal thickness was measured in M-scanning at mitral valve level (mean = 11 mm) and near the cardiac apex (mean = 17 mm). The most striking increase in septal thickness was observed from 10–25 mm and in septal amplitude of motion from 3–15 mm. In real-time B-scanning the characteristic "see-saw" motion was observed in all patients, with a fulcrum at various levels within the interventricular septum even without an increase in right ventricular internal diameter.

It is suggested that increasing apical septal amplitude of motion and thickening should be included into the M-scan criteria of right ventricular volume overload. In addition to these, real-time B-scan criteria should also include the "see-saw" motion with or without increase in left ventricular internal diameter. It is postulated that selective increase in apical septal hypertrophy may be the result of longstanding stroke work of the lower septum to compensate for the haemodynamic loss of the reversed upper septal motion ("RUSM"), thus serving as a differential diagnostic sign in right ventricular volume overload of recent onset.

BEAT TO BEAT VARIATION OF AORTIC VALVE LEAFLETS' PEAK VELOCITIES IN CONGESTIVE CARDIOMYOPATHY AND LOW OUTPUT IN CORONARY ARTERY DISEASE

By H. H. Schmitz, R. K. Oxenham and K. H. Parker

Division of Cardiovascular Disease Clinical Cardiology, Hammersmith Hospital and Physiological Flow Studies Unit, Imperial College, London

Are aortic valve leaflets' peak velocities a guideline in differentiation of congestive cardiomyopathy and low output in coronary artery disease (angiographic EF 50–25%)? The instantaneous positions of anterior and posterior echo of aortic root walls and two aortic valve leaflets (AVL) were traced manually from continuous M-mode echocardiograms (100 mm/s; 1: 2.5 scale magnification). Using a photoelectric curve follower, multichannel tape recorder and multiplexing analogue-to-digital converter these traces were analysed numerically and plotted with their first derivative by a digital computer. In 12 normal subjects AVL-velocities showed little variation (7–12 beats analysed) for opening (2.86±2.74) at 53.20±12.06 cm/s peak opening velocity and for closing (3.25±3.95) at 40.20±9.82cm/s max. closing velocity from beat-to-beat. Twelve patients with COCM showed a higher beat-to-beat variation for AVL-opening (10.09±3.30) at 43.76±7.66 cm/s peak opening velocity and for closing a similar (3.67±1.65) beat-to-beat variation at 29.03±10.69 cm/s max. closing velocity than normal subjects. In 14 patients with low output in coronary artery disease beat-to-beat difference (27.24±14.96) at 54.63±20.40 cm/s peak opening and (21.20±18.33) at 36.50±13.48 cm/s max. AVL-closing velocity was significantly higher ($p < 0.01$) than in the previous groups. Thus beat-to-beat variation of AVL-peak velocities derived from routine echocardiograms contribute to differentiation of COCM from low output in CAD. To study the reduced systolic forward motion (0.61±0.22 cm) in low output in contrast to 1.35±0.22 cm of the normal subjects a linear real-time scanner (VIDOSON^{R}) was used to show the aortic root motion simultaneously with the motion of the interventricular septum, the mitral valve and the left atrium in a longitudinal plane of the heart. In the normal subjects the aortic root was continuous to the septal echo-band at an angle of not smaller than 170° and inward motion of the septum was closely followed by systolic forward motion of the aortic root echo-bands. Patients with low output and dilated ventricle showed smaller angles (140±15°) and a more convex shape of the septum and posterior displacement of the mitral valve. Inward septal motion in these cases was followed by a limited systolic forward motion of the aortic root.

CLINICAL USE OF DISTANCE AND AMPLITUDE MEASUREMENTS IN OPHTHALMIC ULTRASONOGRAPHY

By W. Buschmann and D. Linnert

University Eye Hospital, Wuerzburg, Germany

Echo distance measurements can be performed best using the A-scan technique. They prove especially helpful in determination and follow up studies of tumour diameters and axial length of eyes. The latter may serve for optical calculations, but more important are clinical follow-up studies of buphthalmos eyes and ultrasound exophthalmometry. The former yields a new criterion for evaluating the course of such patients: continued pathologic growth of axial length would indicate insufficient control of the intraocular pressure even if it should be found normal at the time of examination. Ultrasound exophthalmometry is a combination of Hertel's optic exophthalmometry and ultrasonic axial length measurement which provides reliable differentiation of protrusion and pseudoprotrusion in unilateral exophthalmos patients, saving many other more expensive examinations.

The echo amplitudes from internal structures of tissues may be examined by serial A-scans or compound B-scans. The amplitudes of distinct surface echoes, however, may better be determined using A-scans because it is much easier in this technique to ensure vertical incidence of the beam.

Any amplitude evaluation depends on comparison with a standard. Steel and glass block echoes are orders of magnitude more intense than echoes from soft tissues like the eye. The echo of a water/carbon tetrachloride interface is in the desired intensity range but very temperature dependent. Citrated blood and sclera echoes prove also to be too inaccurate. We use now the surface echoes of flat poly-HEMA test reflectors as reference signals. This is the material from which soft corneal contact lenses are made (hydroxyethylmethacrylate). It is available with 38 and 72% water content. The corresponding delta dB figures for sclera, retina, vitreous opacities and intraocular foreign bodies prove very useful in diagnostic work.

3-D MULTIPLANAR SCANNING PRINCIPLES

By T. G. Brown

Sonicaid Ltd. Firth Rd. Livingston, Scotland

In a Multiplanar Scanner the ultrasonic probe is free to be moved in three dimensions over the body contours, with all its movements measured and relayed to the display system. Unlike a conventional scanner, in which the user can select only a single *plane* at any one time by moving the scanner mechanics over the patient, the user of the Multiplanar Scanner can select any suitable viewing *direction* (by means of a small desk-top control). From this viewpoint he can cause a number of separate scans, in different positions on the patient, to build up into a composite image, with each constituent scan seen in its correct relative position. Alternatively, detailed volume scans of particular regions can be made by careful "painting-in" with the exploring sound beam.

Since display screens are themselves two-dimensional in nature, problems can arise in distinguishing overlapping echo patterns. In the Multiplanar Scanner this difficulty can be avoided. A pair of images can be generated simultaneously, which are coded electronically to correspond to the images which would be produced from viewpoints separated by the separation of the eyes. By means of a very simple viewer, these images can be fused in the observer's brain to give a very realistic and convincing three-dimensional image of the distribution of the reflecting structures within the patient.

While having a broad general-purpose capability, the system is particularly suited to making high-resolution images of complex anatomy or pathology, where two-dimensional techniques are less effective.

THE ULTRASONIC SIGNS OF FETAL DEATH IN THE FIRST TRIMESTER

By G. B. Young

Department of Radiodiagnosis
Simpson Memorial Maternity Pavilion and
The Royal Infirmary, Edinburgh

The principal ultrasonic signs of death of the fetus in the first 12 weeks of pregnancy were reviewed and illustrated. Although as shown by Robinson (1972) the cardinal sign of fetal death is failure to demonstrate the fetal heartbeat, with the advent of grey scale ultrasound other positive signs are now available and of practical use.

Three commercial ultrasonic machines were used in this study – the Kretz and Sonicaid systems were grey scale only, the Diasonograph 4102 was dual and permitted the use of either grey scale or a bistable display. The Sonicaid system had 3-D facilities. The 3-D system of imaging greatly enhanced the study of the implantation site and development of the gestational sac and its covering of chorionic trophoblast. It was observed that in the fifth week of amenorrhoea the sac often appeared empty and was shaped like a signet ring – the signet of the ring being the embryonic pole and containing the feto-placental complex.

Three new signs of death were described. An empty sac with a well developed feto-placental complex adjacent to the sac wall, and a sac with no fetal bud but containing "floating" debris in a fluid level, were both indicative of a failed pregnancy. In the later weeks of the third trimester a long linear intra-uterine echo, presumably due to a gas bubble (CO_2) in the fetus itself or its umbilical cord, was good presumptive evidence of a missed abortion. The differential diagnosis between a failed pregnancy, hydatidiform mole and an ectopic pregnancy was briefly discussed and illustrated.

REFERENCE

ROBINSON, H. P., 1972. Detection of fetal heart movement in the first trimester of pregnancy using pulsed ultrasound. *British Medical Journal*, *4*, 466–468.

24 HOUR STUDIES OF FETAL RESPIRATORY MOVEMENTS (FRMS) AND FETAL BODY MOVEMENTS (FBMS) IN NORMAL AND ABNORMAL PREGNANCIES

By A. B. Roberts, D. Little and S. Campbell

King's College Hospital, Denmark Hill, London

Twenty-one women were studied over 24 hour periods using an ADR* real-time scanner. A total of eight hours recording of FRMs and FBMs was made in each patient. Sixteen patients had normal pregnancies, and five had growth-retarded fetuses as determined by serial ultrasound measurements. Three had asymmetrical growth-retardation with the abdomen circumference lower than the 5th centile limit, and a head/abdomen ratio above the 95th centile limit; while two had symmetrical growth-retardation with both head and abdomen circumference below the 5th centile limit.

The 24 hours were split into eight three-hour sessions, during which recordings were made for one hour in each. The women lay in the left lateral position and the transducer was set to show a transverse section of the fetal abdomen. It was held in place using a clamp designed by Kretz Technic. Each breath, and the beginning and end of each fetal movement, was punched directly on to computer tape. Blood samples were taken in the middle of each hour's recording and three-hourly urine samples collected. In the normal pregnancies FRMs were present for a mean of 30% of the time (range 11–61%), the incidence being greater later in gestation. There was a marked diurnal variation with FRMs being least in late evening and early morning. There was a significant correlation between FRMs and blood glucose levels ($p < 0.003$) and urinary catecholamine levels ($p < 0.01$); but not between FRMs and plasma catecholamines, cortisol, or oestriol. FBMs were present for a mean of 20% of the time (range 11–26%), and were greatest in late evening and early morning. In the asymmetrical growth-retarded fetuses the FRMs (mean 9%) and FBMs (means 8%) were significantly less. In the symmetrical growth-retarded fetuses FRMs and FBMs were in the normal range.

---

*Tempe, Arizona.

Proceedings of The British Medical Ultrasound Society

ULTRASONIC SCANNING IN SUSPECTED ECTOPIC PREGNANCY

By Jan Fog Pedersen and Rene Fiege

Ultrasonic Laboratory, Department of Obstetrics and Gynecology, Rigshospitalet, Tagensvej 18, DK 2200 Copenhagen N, Denmark

Quite often the diagnosis of ectopic pregnancy is rather obvious, and the patient can be taken directly to laparoscopy and/or surgery, laparoscopy being a well accepted diagnostic modality in suspected ectopic pregnancy. With only slight suspicion, however, a noninvasive means of selecting patients for laparoscopy is desirable.

We report on 27 consecutive patients to ultrasonic scanning for suspected ectopic pregnancy. The ultrasound report was no sign of ectopic pregnancy in 21 cases, ectopic pregnancy was not ruled out in four cases, and was proven in two cases. Follow-up showed that only the two latter patients actually did have an ectopic pregnancy. Thus, in this admittedly small series of patients with slightly to moderately suspected ectopic pregnancy, ultrasound was able to demonstrate the few cases of ectopic pregnancy, and to rule out this condition in a large proportion of the remaining patients.

A COMPARISON OF BIPARIETAL MEASUREMENTS USING A REAL TIME SCANNER AND A CONVENTIONAL SCANNER EQUIPPED WITH A CODED CEPHALOMETRY SYSTEM

By A. H. Adam, H. P. Robinson, A. J. Hall and J. E. E. Fleming

Department of Ultrasonics, Queen Mother's Hospital, Glasgow

The determination of the fetal biparietal diameter by means of an ultrasonic examination provides, in early pregnancy, an index of gestational age, and, later in pregnancy, on a serial basis, an index of fetal growth rate. With the advent of the more portable real-time scanner, the potential now exists for examining patients in the antenatal clinic. However, with the hand-held transducer employed with this type of equipment, Campbell's method of cephalometry cannot be applied directly.

A trial was performed to assess the accuracy of BPD measurements obtained using a real time scanner (Diagnostic Sonar, System 85) and a conventional scanner (Nuclear Enterprises Diasonograph NE 4102) equipped with a coded cephalometry system. This coded system provides 30 different coding constants, arranged in a random fashion, and displays a number related to the real value according to the unknown coding constants. This approach enables the operator to interact with the caliper display and follow normal measuring procedure.

The largest of the three coded readings of a biparietal measurement was compared with that obtained using the real time scanner. The distribution of the differences between readings was satisfactorily narrow and, of the total casse, 69% lay within ± 2 mm. Where the subjective assessment of the reading obtained using the real time scanner was classified as "good", 90% were within ± 2 mm. and all within ± 3 mm, of the Diasonograph measurement. The average time taken for the real time measurement was approximately one third that of the conventional scanner.

THE PREDICTION OF BIRTHWEIGHT IN THE BREECH FETUS

By V. Poll

Department of Clinical Physics
Southampton General Hospital

The breech fetus at term sometimes presents the obstetrician with a difficult choice as to the proposed method of delivery. In making his assessment he has to consider many factors, among the most important of which are gestational age and estimated fetal weight. Both of these factors can be assessed using standard ultrasound techniques, the bi-parietal diameter and fetal abdominal circumference measurements respectively. Problems associated with these techniques, and some methods of avoiding them, are discussed. These appear to be a function of each particular unit where the investigations are performed. This paper presents results from a still-continuing trial where the estimated weight from ultrasound measurements was compared with that at delivery. Although calibration data differ from those of other workers, and the breech presentation itself presents mensuration problems, provisional results indicate that the accuracy of weight prediction is as good as ±270 g (±2 S.D.) in a well-defined sub population.

ANTE-NATAL SCREENING FOR NEURAL TUBE DEFECTS

By A. D. Christie and W. G. Millar

Perth Royal Infirmary

As present day knowledge does not indicate that fetal malformation can be prevented, it is of the utmost importance that methods are found which will identify malformations while abortion is still feasible. A recent Lancet article (Lancet 1977) reported the results obtained from a UK collaborative study, involving nineteen centres, on maternal serum alpha feto protein levels in ante-natal screening for defects of the neural tube in early pregnancy. It is evident from the report that detection of anencephaly and *open* lesions only was feasible, but detection rates were disappointing unless further testing of amniotic AFP was carried out on selected patients. The selection must be done by establishing a "cut-off" point below which no further testing is done. As there is a considerable overlap, the "cut-off" point must be a compromise, resulting in many normal fetuses registering levels above this point, which leads to needless anxiety and further unnecessary testing and possibly mistaken termination of pregnancy. Similarly, many abnormal fetuses will register *normal* limits and will consequently be excluded from further testing. Furthermore, the validity of the serum AFP test is greatly dependent upon knowledge of the gestational age of the fetus. In our experience, this cannot always be calculated reliably from knowledge of the mother's last menstruation. It is suggested in the Lancet article and others (Bond *et al.*, 1977; Clark *et al.*, 1977), that ultrasound could be used to check the gestation if the serum results are "high". It is our contention that a more effective method of detecting fetuses with neural tube defects may be by routine ultrasound examination of all patients in early pregnancy (18 weeks gestation, as determined by ultrasound). This method is infinitely less costly, less complicated, and entirely acceptable to the patient. Anencephaly can be positively identified in all cases, and gross spina bifida detected by careful scanning of the neural tube. It is conceded that a minor degree of spina bifida may well be difficult or impossible to identify, but this may be correctible surgically with no subsequent handicap.

We have conducted a total population screening programme for more than two years with encouraging results. In a total of 3,050 patients screened specifically for neural tube defects at 18–20/52 gestation, 11 cases with neural tube defects were found as follows: total no. screened 3050; anencephaly 5; anencephaly and spina bifida 1; spina bifida 1; iniencephaly 1; hydrocephaly 3. In addition, one further case of severe hydrocephalus was found in a patient who reported for the first time to our clinic at 30 weeks gestation. This fetus also had a lumbar spina bifida which was not diagnosed. There were no other cases of neural tube defects amongst the screened population.

We feel that ultrasound screening of all pregnancies around 19/52 *known* gestational age is a reliable and acceptable technique of screening for neural tube defects and probably superior to other methods currently available.

REFERENCES

The Lancet. June 25 1977. Maternal serum-alpha-fetoprotein measurement in ante-natal screening for anencephaly and spina bifida in early pregnancy. Leading Article.

BOND, E. B., THOMPSON, W., and ELWOOD, J. H., 1977. Evaluation of measurement of maternal plasma alpha-fetoprotein levels as a screening test for fetal neural tube defects. *British Journal of Obstetrics and Gynaecology*, *84*, 574–577.

CLARK P. C. 1977. Screening for fetal neural tube defects by maternal plasma alpha-fetoprotein determination. *British Journal of Obstetrics and Gynaecology*, *84*, 568–573.

A REVOLUTION IN RESOLUTION

By Hylton B. Meire

Clinical Research Centre, Harrow

During the three years since the introduction of grey scale display on commercial ultrasound scanners there has been a progressive improvement in both the grey scale performance and resolution capability of these machines. The introduction of higher frequency, internally focussed transducers has brought about a particularly dramatic improvement in resolution. The changes that have occurred over the last three years are documented by reviewing material collected during that period. The images shown include demonstration of the normal biliary tree, intra renal vessels and medullary structure, detailed fetal anatomy the normal pancreas and third generation branches of the coeliac axis. The implications of these developments for clinical diagnosis and the likely future improvements are discussed.

THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE BY MEANS OF GREY-SCALE ULTRASOUND B-SCAN

By J. M. G. Chu, D. O. Cosgrove and V. R. McCready

Department of Nuclear Medicine & Ultrasound, Royal Marsden Hospital, Sutton, Surrey

The differential diagnosis of jaundice is an important clinical problem. Surgery in the case of hepato-cellular disease is dangerous because it is associated with a greatly increased mortality rate. Percutaneous liver biopsy in post-hepatic obstruction has the added risks of biliary peritonitis and septicaemia.

In a prospective study of 100 jaundiced patients, whose diagnoses were subsequently made at laparotomy or on liver biopsy, 94 were correctly categorized. There were five errors and one failure. There were 47 correct diagnoses in 51 obstructions of which 30 had the level precisely located and the pathology identified. Of the 49 hepato-cellular disorders, 47 were correctly identified and 31 had abnormal echo-pattern. These were seen in cirrhosis, tumour infiltration and chronic active hepatitis. The overall success rate compares more than favourably with the currently available invasive techniques although, for precise anatomical localization, an added procedure is probably required where ultrasound has failed to define this on a second attempt. As a non-invasive procedure, ultrasound B-scanning should be the investigation of choice for the differential diagnosis of jaundice. Diffuse hepato-cellular disorders may also be correctly categorized.

THE USE OF ULTRASOUND AND HIDA IN THE INVESTIGATION OF JAUNDICE

By A. E. A. Joseph, K. C. Dewbury, D. M. Ackery N. W. Garbie and P. McGuire

Southampton General Hospital, Southampton

Biochemical and the more simple radiological investigations do not distinguish between hepatocellular and obstructive jaundice in a significant proportion of patients. The IVC is usually unsuccessful when the bilirubin level is above 3mg%. Ultrasound and HIDA studies in our experience have shown that the more invasive procedures, such as percutaneous transhepatic cholangiogram and ERCP, may be dispensed with in many instances.

We have found that an ultrasound examination establishes the presence of obstructive jaundice in nearly 100% of patients and frequently indicates the level and cause. The diagnosis of hepatocellular jaundice is made in the absence of dilated ducts and in certain instances from the characteristic echo pattern in the liver. Ultrasound may not always be successful, does not distinguish between partial and total obstruction, may not detect very early obstruction and will not distinguish persistent dilatation of the ducts after relief of obstruction from continuous obstruction. We have noted that HIDA studies will, in most instances, distinguish between total and partial obstruction, detect early obstruction and often demonstrate the level. Early hepatocellular jaundice shows a patchy liver uptake with demonstration of the common bile duct and the passage of activity into the gut. In the more severely jaundiced patients, similar appearances are obtained in both hepatocellular jaundice and total obstruction. The ultrasound examination will, however, invariably distinguish between these.

STUDIES IN CANCER TREATMENT WITH ULTRASOUND

By F. W. Kremkau

Bowman Gray School of Medicine,
Wake Forest University,
Winston-Salem, N. C. 27103, USA

The potential use of ultrasound in cancer therapy has been studied by several investigators over a period of 45 years. There have been three approaches to the subject: studies of effects on tumours with (1) ultrasound alone, (2) ultrasound in combination with radiotherapy, and (3) ultrasound in combination with chemotherapy. In area (1) varying results have been reported. In some cases, decreased growth rates or regressions of tumours have been reported, but, with others, no effect was observed or growth rate was increased. In area (2), for some animal tumours, combined treatment gave a greater effect on the tumours than that produced by x-ray alone, while, in others, addition of ultrasound produced no change. In area (3), drug enhancement has been observed in melanoma and in mouse tumour cells treated with ultrasound and several anticancer drugs. Mechanisms of action in these experiments are not fully known.

Studies at our institution have revealed the following: *in vitro* ultrasound treatment (2.2 MHz, 10 Wcm^{-2} for 10 minutes) of mouse leukemia L1210 cells in drug suspension enhances cytotoxicity of five (actinomycin-D, busulfan, daunomycin, methotrexate, vincristine) out of ten cancer chemotherapy agents studied. Some evidence is available to suggest that this enhancement does not result from plasma membrane permeability alteration. *In vivo* ultrasound treatment (2.2 MHz, 1.5 Wcm^{-2} for 15 minutes of S180 mouse sarcoma implanted subcutaneously in hind limbs reduced the TCD_{50} by 40%. A similar study with C3H mammary carcinoma resulted in no change in TCD_{50}. There is evidence that the TCD_{50} reduction in S180 is consistent with a thermal mechanism of action hypothesis. The potential of ultrasound to provide local tumour control or enhancement of other therapy modes motivates the current effort by several groups to study and understand further its action on malignancies.

REAL-TIME IMPROVEMENT OF LATERAL AND RANGE RESOLUTION BY OPTICAL SIGNAL PROCESSING

By J. C. Somer

Biomedical Center, University of Limburg, Maastricht, The Netherlands

Present attempts at digital-computer processing as applied to fast scanning systems are based on processing the signals as a function of time and cannot be performed in real time. Coherent optical computers are able to achieve an enormous data-processing rate that may be of the order of 10^{12} bit per second. An advantage of paramount importance in this respect is the capability of such systems to perform the operations in two dimensions. This opens very promising prospects towards simultaneous filtering in time *and* in space. Real time processing, in order to improve both range and azimuthal resolution and possibly signal-to-noise ratio of fast scanning systems is of utmost importance in ultrasound diagnostics, particularly in visualizing dynamic structures like the heart or pulsating arteries.

Optical frequency plane matched filtering yields an output signal which is the cross-correlation function between received signals (echoes) and a replica of a standard signal, which may be the echo received from a reference (point) target. Therefore a light modulating system is used that converts the echo signals in optically modulatable form in the xy-plane of the optical computer. Since the method is applied to a phased-array system, not only time information is available at reception but also space information. The mapping in the xy-plane takes place instantaneously and continuously. If the xy-plane is illuminated by a coherent monochromatic light-source, a lens-system, having this xy-plane in its first focal plane, will map the Fourier-transformation $S\ (f_x,f_y)$ of the signal $s\ (x,y)$ in the second focal plane, which is also called the frequency plane. In order to perform frequency plane matched filtering a transparency is required which contains the complex conjugate spectrum $S^*\ (f_x,f_y)$, assuming that $S\ (f_x,f_y)$ is the spectrum of the reference signal $s\ (x,y)$, being the echo of a reference (point) target. In 1964 Van der Lugt published a method for realizing such a filter by holographic means.

A hologram made of the spectrum $S\ (f_x,f_y)$ contains both the original spectrum and its complex conjugate, which are diffracted off-axis at opposite diffraction angles. If this transparency coincides accurately with the time-variable spectrum of the received signals $s'(x,y)$, one of the two diffracted portions represents the product of $S'(f_x,f_y)$ and $S^*\ (f_x,f_y)$. A second lens-system is then used to make the inverse Fourier-transformation. The x′y′- output plane now shows an output signal $s_o\ (x',y')$ which is the cross correlation between $s'\ (x,y)$ in the input plane and the reference signal $s\ (x,y)$. Every time the signals $s'\ (x,y)$ contain a signal $s\ (x,y)$ the auto-correlation function of $s\ (x,y)$ appears. *In vitro* a considerable real-time improvement in resolution has been obtained, both in range and in azimuth.

A COMPARISON OF GREY SCALE RECORDING MEDIA

By Hylton B. Meire

Clinical Research Centre, Harrow

Coincident with the rapid proliferation of grey scale ultrasound equipment and computerized X-ray scanners, there has been an increase in the number of different types of image recording devices. Basically, six different systems are now available and have widely different costs and performances, several being both expensive and inadequate. We have compared the cost, convenience, grey scale range and reliability of eight separate systems and attempted to determine which is most suitable. 35 mm photography is cheapest both in capital and running costs but is least convenient, whilst the Video Hard Copier is most convenient but has the worst grey scale performance. Each system has its own particular advantages and these are discussed and compared.

ULTRASONIC IMAGE STORAGE AND MANIPULATION BY MICROPROCESSOR

By P. T. Ostro and L. Harrison

Department of Electrical and Electronic Engineering, University of Nottingham, Nottingham NG7 2RD

Conversion of oscilloscope, grey-scale B-scans to TV format is usually performed by means of scan converter tubes. However the technology of the scan converter tube requires there to be careful maintenance in order to retain peak performance. As an alternative, a digital scan converter has been constructed which after initial setting up, should require little further attention.

At present the resolution of the system is 128 × 128 picture cells, each of which can store 16 levels of grey. Data is first stored in static RAM (random access memory) and then transferred to a CCD (charge coupled device) memory system. The latter memory system, being dynamic, is clocked in such a way as to produce a signal which, when passed through a suitable analogue to digital converter, is used to form a composite TV signal. Since two CCD stores are used, two complete pictures may be stored.

Once a digital picture has been obtained it is then logical to link this to a computing system of some kind. A microprocessor (Intel 8080) is used in the present system.

The computing capability then allows image processing to be performed by writing suitable software. The design of the system also allows any type of response curve to be used linking echo amplitude to image intensity, and this facility, linked with the microprocessor, allows the system to optimize its own response for any particular B-scan.

COMBINING VESSEL IMAGING AND BLOOD VELOCITY MEASUREMENT

By P. J. Fish, I. M. Wilson, T. I. H. Brown
B. Deakin and M. Barrett

Physics Department, King's College Hospital, London

It is now nearly two decades since the introduction of the ultrasonic Doppler blood flow detector. It has been realized for most of that time that Doppler ultrasound has the potential for non-invasive, transcutaneous blood velocity and flow measurement. It is however only recently that there have been signs of the potential being realized.

The use of a multichannel pulsed Doppler instrument with an imaging facility allows not only lateral, antero-posterior and cross-sectional images of vessels to be generated but the imaging facility also enables two of the problems associated with velocity measurement to be overcome.

Firstly the beam/vessel angle can be easily measured from the stored co-ordinates of an imaged section of vessel, so allowing velocity to be related to measured Doppler shifts and secondly the beam can be directed through a chosen part of a vessel and maintained in position while the velocity measurements are made.

Deconvolution of measured velocity profiles is necessary when the size of the sampling volume of the pulsed Doppler instrument is comparable with the diameter of the vessel.

The result of these procedures is an image of the lumen of the vessel of interest together with velocity profile from which the flow rate can be calculated.

Acknowledgment

The authors are grateful to the Department of Health and Social Security and GEC Medical Equipment Ltd for funds to carry out this work.

A REAL-TIME B SCAN/PULSED DOPPLER SYSTEM FOR FETAL BREATHING AND OTHER OBSTETRICAL STUDIES

By T. Anderson, W. N. McDicken, R. McHugh
and C. R. Bow

Department of Medical Physics, Royal Infirmary
Edinburgh

K. Boddy, R. Cole, P. Thomson and G. B. Young

Simpson Memorial Maternity Pavilion, Edinburgh

The requirements of an ultrasonic system for fetal breathing studies are discussed. A system has been constructed which allows the fetus to be observed, using a real-time scanner, and activity to be monitored over longer periods, using a pulsed Doppler unit or an A-scan plus T-M scan recorder. Examples of results obtained with this system are presented. The equipment can also be employed more widely in obstetrics, for example to study the fetus in each trimester of pregnancy or structure movement and blood flow in the fetal heart. Preliminary results in these areas are indicated.

PHYSIOLOGICAL SIGNIFICANCE OF BLOOD-VELOCITY/TIME WAVEFORMS RECORDED FROM NORMAL AND DISEASED ARTERIES, USING DOPPLER SHIFT FLOWMETERS

By R. Skidmore and J. P. Woodcock

Department of Medical Physics
Bristol General Hospital

Ultrasonic flowmeters have been used for a number of years to study arterial disease. The shape of the blood-velocity/time waveforms recorded at the common femoral, popliteal and posterior tibial arteries in the leg, for example, can distinguish between partially and totally occluded atherosclerotic vessels (Woodcock 1970, Gosling and King 1975). More powerful methods have now been developed for studying the femoral-popliteal-posterior tibial arteries which used the blood-velocity/time waveform recorded at the common femoral as the input waveform to the segment and the posterior tibial blood-velocity/time waveform as the output. The artery between the two probes is considered as a black box, and no assumptions are made about its properties except that they can be described by linear mathematics. Morris and colleagues (1976) have shown that the transfer function for the normal and diseased vessels can accurately be described by a transfer function of the form:

$H(s)=(1+A_1S+A_2S^2)/(b_0+b_1S+b_2S^2+b_3S^3)$

In both normal and totally occluded arteries, with a collateral circulation, there are two zeros and three poles. In the present study the physiological significance of the positions of the poles of the transfer function are being investigated with the help of an analogue circuit which synthesises this type of transfer function. Using techniques such as these it may be possible to "fingerprint" the action of a drug on the peripheral circulation by being able to distinguish between changes in vasoconstriction/vasodilatation and changes in elasticity, using information gained non-invasively.

REFERENCES

GOSLING, R. G. and KING, D. H. 1975. In *Arteries and Veins* edited by A. W. Harcus and L. Adamson (Churchill-Livingstone), 61–84.

MORRIS, S. J. OWENS, D., PAYNE, P., WELLS, P. N. T. and WOODCOCK, J. P. 1976. *IERE Proceedings Electronics in Medicine*, p.230–247.

WOODCOCK, J. P. 1970 Ph.D. Thesis, University of London.

ASSESSMENT OF ABNORMALITIES IN CARDIAC OUTPUT BY TRANSCUTANEOUS AORTOVELOGRAPHY

By L. H. Light

Clinical Research Centre, Watford Road, Harrow
Middlesex

Non-invasive measurements of mainstream aortic blood velocity by transcutaneous aortovelography (TAV), (Light, 1977; Cross and Light, 1974) have been shown to be reproducible (Frazer *et al.*, 1976) (SD=7%) and closely proportional to central blood flow (Sequeira *et al.*, 1976) (SD=13%) over a considerable range of stroke volumes. The technique thus offers a convenient way of quantitating changes in body perfusion and left heart function, with applications in intensive and coronary care (Buchthal *et al.*, 1976). In addition, analysis of changes under stress and of waveform abnormalities (Light 1977) is proving useful in cardiology, *e.g.* for the measurement of regurgitant fraction in aortic incompetence.

Absolute cardiac output could not, however, be calculated with adequate accuracy from TAV measurements and an aortic diameter by assuming a circular cross-section and perfectly flat flow profile (Sequeira *et al.*, 1976). Nevertheless, normality or otherwise of systemic flow can be deduced from individual velocity readings from a knowledge of the normal range: the remarkable constancy of peak systolic blood velocity in children from one to 12 years of age (Beardshaw *et al.*, unpublished) (SD of age group means from childhood mean = 3%) suggests that vascular dimensions are controlled during development so as to keep blood velocity within a certain physiological range. Subsequent departure from this – other than a gradual decrease in velocities with age in the over 30's – appears to indicate pathological change.

The standard deviation (from the age-dependent mean) for TAV measurements is 17% compared with an SD of 12% quoted for cardiac index. In the absence of pathological deformation of the aorta (Light 1976a) abnormalities of body perfusion can therefore be non-invasively assessed by TAV with a sensitivity which is little inferior to actual measurements of cardiac output, while waveform changes give further—and often more specific—information about left ventricular function (Light 1976b).

REFERENCES

BEARDSHAW, J. A., SHINEBOURNE, E. A. and LIGHT L. H. Transcutaneous aortovelography—normal values in children. (Unpublished).

BUCHTHAL, ANNA, HANSON, GILLIAN C., and PEISACH, A. R., 1976. Transcutaneous aortovelography—potentially useful technique in management of critically ill patients. *British Heart Journal*, *38*, 451–456.

CROSS, G., and LIGHT, L. H., 1974. Non-invasive intrathoracic blood velocity measurement in the assessment of cardiovascular function. *Biomedical Engineering*, *9*, 464–471.

FRAZER, C. B., LIGHT, L. H., SHINEBOURNE, E. A., BUCHTHAL, ANNA, HEALY, M. J. R., and BEARDSHAW, J. A., 1976. Transcutaneous aortovelography—reproducibility in adults and children. *European Journal of Cardiology*, *4*, 181–189.

LIGHT, L. H., 1976a. Non-invasive haemodynamic flow measurement techniques for routine clinical use. In *Applications of Electronics in Medicine*, pp.21–38, Institution of Electronic and Radio Engineers (Conf. Publication 34), London.

1976b. Transcutaneous aortovelography—a new window on the circulation? *British Heart Journal*, *38*, 433–442.

1977. Aortic blood velocity measurement by transcutaneous aortovelography and its clinical applications, in: *Echocardiology*, Ed: N. Bom, p.233–243 (Martinus Nijhoff, The Hague).

SEQUEIRA, R. C., LIGHT, L. H., CROSS, G., and RAFTERY, E. B., 1976. Transcutaneous aortovelography—a quantitative evaluation, *British Heart Journal*, *38*, 443–450.

ATTENUATION OF ULTRASOUND IN NORMAL AND ISCHAEMICALLY INJURED MYOCARDIUM

By J. G. Miller

Washington University, St. Louis, Missouri, USA

This study was undertaken in an effort to identify the mechanisms responsible for the attenuation of ultrasound in myocardium and to assess the potential of ultrasound as a means of characterizing the state of myocardial tissue. Results of a series of measurements *in vitro* on approximately 600 sites from more than 60 dogs are presented which contrast attenuation in normal and ischaemically injured zones of tissue from animals sacrificed 15 min, 1 hr, 6 hr, 24 hr, three days, two weeks, and six weeks following coronary ligation. To measure the frequency dependence of the attenuation in myocardium, broadband pulses (2 to 10 MHz) were transmitted through tissue using a transducer configuration designed to minimize ultrasonic phase cancellation effects, a potential source of artifact in attenuation measurements. The freshly excised tissue was maintained at 20°C, a temperature selected to prevent significant degradation during the time required to carry out the measurements. Ischaemic injury or infarction was produced in adult dogs by ligating the left anterior descending coronary artery immediately distal to the first ventricular branch. For dogs sacrificed from 15 minutes to six hours following occlusion, colloidal carbon black was injected into the left atrial appendage fifteen seconds prior to killing the animal to differentiate regions of ischaemic and normal myocardium. The region of ischaemia did not change colour after injection while the region of normal flow rapidly was stained black. Tissue from animals sacrificed 24 hr, and three days following occlusion was analyzed biochemically for creatine kinase (CK) content, an established index of myocardial tissue pathology. Tissue from dogs sacrificed two weeks and six weeks following coronary occlusion was analyzed for collagen content using a biochemical assay based on hydroxyproline.

Results of these investigations document a small decrease in the attenuation of ischaemic myocardium as compared with that of normal for tissue studied 15 min, 1 hr, 6 hr, and 24 hr following coronary occlusion. This decrease in attenuation might be associated with oedema. In contrast, an increase in the attenuation of ischaemically injured tissue relative to that of normal is observed at three days, two weeks, and six weeks following occlusion. The increased attenuation is associated with scar formation, as documented by good correlation between ultrasonic attenuation and collagen concentration in the two-week and six-week groups. Theoretical considerations suggest that mechanisms associated with the microscopically inhomogeneous nature of soft tissue, especially viscous relative motion losses, can account for a substantial fraction of the attenuation observed in normal and ischaemically injured myocardium.

THE DIFFRACTION OF ULTRASOUND BY HUMAN TISSUES: A CLINICAL TOOL?

By D. Nicholas

Institute of Cancer Research, Royal Marsden Hospital Sutton, Surrey

The use of ultrasound in clinical diagnosis has involved, primarily, its imaging capabilities by displaying the backscattered echoes originating from inhomogeneities within soft mammalian tissues. It is only in the past few years that a concerted effort has been made to examine the scattered echoes on a more physical basis.

Our investigations into the interaction of ultrasound and biological tissues have concentrated on the diffractive nature of scattering. We have shown (Nicholas and Hill, 1975a and b) that *in vitro* investigations utilizing diffraction at preset frequencies enable us to characterize specific tissue types and pathologies and also permit the assessment of some macroscopic tissue structures. More recent reports (Nicholas 1976; Huggins and Phelps, 1977) indicate how such techniques have been implemented clinically. This paper reviews our current clinical findings and assesses the usefulness of our techniques. Future developments, and the general role of diffraction in clinical diagnosis are discussed.

REFERENCES

NICHOLAS, D. and HILL, C. R., 1975a. Acoustic Bragg diffraction from human tissues. *Nature*, *257*, 304–306.

1975b. Tissue characterization by an acoustic Bragg scattering process. In *Ultrasonics International, 1975*, 269–272 (IPC Science and Technology Press, London).

Nicholas, D., 1976. The application of acoustic scattering parameters to the characterisation of human soft tissues. *Proceedings 1976 IEEE Ultrasonics Symposium*, Cat. 76 CH1120–5SU.

Huggins, R. W. and Phelps, J. V., 1977. Bragg diffraction scanner for ultrasonic tissue characterization *in vivo*. *Ultrasound in Medicine and Biology*, *2*, 271–277.

TIME ANALYSIS OF ECHOGRAMS BY COMPLEX DEMODULATION

By R. Kruizinga and J. M. Thijssen

Biophysics Laboratory, Institute of Ophthalmology
University of Nijmegen, Philips van Leydenlaan 15
Nijmegen 6804, The Netherlands

Clinical echography is generally based on a visual evaluation of the various aspects of the demodulated echogram, *i.e.* the time of occurrence, the motility and the amplitude of the individual echoes. Analysis of the quantitative aspects concerning the amplitude is essentially limited by the rectification of overlapping echopulses before the display at the oscilloscope. As a first approximation the echogram can be described as the result of a convolution of a series of δ-pulses with a reference echo. The method of choice to determine the time of occurrence and the amplitude of echoes should be the method of inverse filtering applied to the RF-signal. The transfer function of the inverse filter is defined as $|S(\omega)|^{-1}$, $S(\omega)$ being the Fourier transform of the reference echo. *In vivo* measured clinical echograms do not fulfill the requirement that, except for an attenuation factor and a time delay, the echoes are identical to the reference. It is, therefore, not adequate to apply inverse filtering methods to the echogram. The complex demodulation technique which will be applied to the RF-echogram makes use of the so-called analytical signal, or pre-envelope $f_p(t)$:

$$f_p(t)=f(t)+j\hat{f}(t) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

with:

$f(t)$ = the original echogram
$j=\sqrt{(-1)}$
$\hat{f}(t)$ = the Hilbert transform of $f(t)$

The pre-envelope is a complex time varying function, which can be described by the modulus and the argument. The modulus, which is the envelope, or demodulated signal, is identical to the "video"-signal at the A-scan oscilloscope (when a linear amplifier is used). The argument can be used to calculate the occurrence time of the echoes. The applicability of the latter method will be illustrated with clinical data. The secondary estimation of the amplitude of overlapping echoes, while making use of the already determined occurrence times, will be outlined.

This work is supported by the Netherlands Organization for Health Research (GO–TNO).

SOME PROBLEMS IN THE CHARACTERIZATION OF ULTRASONIC TRANSDUCERS

By J. C. Gore and S. Leeman

Department of Medical Physics, Hammersmith Hospital
London

Proper descriptions of the ultrasonic fields produced by the transducers used for biomedical applications are important for quantitative comparisons of equipment. Results of different investigators, and some of the problems involved in the characterization of transducer radiation patterns, are discussed. The transient sound field from a plane transducer is described, and some of the design factors that become more important with increasing band width are discussed. The significance of the various quantities that may be measured is assessed, with particular relevance to the evaluation of transducer imaging capabilities in A and B scanning. Some of the limitations of presently accepted techniques of evaluating transducers (using test objects) are outlined, and an alternative approach based on the use of transducer transfer functions is proposed. The use of transient pulsed fields is shown to complicate an accurate description of both A and B scanning, but useful quantitative criteria for resolution and related quantities may be derived from measured transducer spatial frequency responses. Further applications and problems involving finite-amplitude effects are mentioned.

WAVEFORM VARIATIONS IN PULSED ULTRASONIC BEAMS – A COMPUTER STUDY

By F. A. Duck

Institute of Cancer Research, Sutton, Surrey

The beams from pulsed transducers used in ultrasonic pulse-echo diagnostic equipment are generally plotted by making multiple echo-amplitude measurements, or by scanning the beam using a miniature hydrophone probe. Under these circumstances the variations in pulse waveform which are observed as the probe or target passes through the beam are ignored and the peak pulse amplitude measured. The fact that the beam differs somewhat from the predicted continuous wave field is noted but generally the CW field is used as an acceptable approximation in the absence of anything better.

The beam can, however, be alternatively described in terms of an impulse response function, that is, the beam which would result from a single abrupt movement of the transducer face. This approach leads to a method by which the pulse shape at any point in the beam may be predicted given a knowledge of the dimensions of the transducer and the characteristics of the transducer oscillation, a method which in addition lends itself to simple implementation digitally. A FORTRAN program has been written which enables these computations to be made for plane piston sources both circular and rectangular in shape. The computations may be carried out to predict the waveform within the beam, the waveform reflected from a point target, or the waveform from a circular plane target.

The pulsed field under all circumstances consists of two or more components which may or may not be separate and distinguishable depending upon the field position and the duration of the transducer oscillation. For instance the pulse from a rectangular transducer may contain up to five components, and that reflected back from a point target to a circular transducer up to six components. Computer predictions of these waveforms will be shown together with a film presenting the changing waveform throughout a pulsed beam under a variety of conditions.

1978, *British Journal of Radiology*, *51*, 653 AUGUST 1978

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

The biliary excretion of the stereo-isomers of iocetamic acid (Cholebrin)

THE EDITOR—SIR,

Iocetamic acid (Cholebrin) is an oral cholecystographic agent which has been in clinical use since 1969 (Owen and Lavelle, 1978). It is marketed as a mixture of dia-stereo-isomers of *N*-acetyl-*N* (3 amino 2,4,6 triiodophenyl) beta-amino-isobutyric acid (Janbroers *et al.*, 1969) in the proportions of 53% (upper limit 59%) of isomer A and 47% (lower limit 41%) of isomer B.

Visualization of the gall-bladder with cholecystographic agents is dependent on their ability to undergo excretion into the bile. We have therefore investigated the stereo-specificity of the biliary excretion of iocetamic acid.

TABLE I

CRITERIA USED IN GRADING FILMS ON CONTRAST DENSITY (after Stanley *et al.*)

Numerical value	Criteria
4	Equal or exceeding opacity of the cortex of the lumbar vertebral pedicle
3	Greater than the opacity of rib but less than four
2	Equal to the opacity of the eleventh or twelfth rib
1	Less than the opacity of the eleventh or twelfth rib
0	Non-visualization

TABLE II

A COMPARISON OF THE SUMMATED SCORES OF GALL-BLADDER VISUALIZATION IN SIX SUBJECTS TAKING STEREO-ISOMERS OF CHOLEBRIN

Subject		Isomer A	Isomer B
1	Control	2	1
	Contrast	13	15
2	Control	1	0
	Contrast	11	10
3	Control	1	1
	Contrast	12	15
4	Control	1	1
	Contrast	16	16
5	Control	0	0
	Contrast	10	11
6	Control	1	1
	Contrast	6	3

Three grammes of the two isomers of iocetamic acid were given on separate occasions, at an interval of one week, to each of six healthy male volunteers aged between 26 and 36 years. A supine oblique control film was taken on each occasion before the isomers were given and a further supine oblique film 14 hours after giving the contrast. They were instructed to refrain from taking fatty foods following iocetamic acid administration.

All identification was removed from the radiographs which were presented separately to four external assessors who graded them in the manner illustrated in Table I (Stanley *et al.*, 1974). The observers scores for each radiograph were summed, giving a maximum possible score of 16 in each case. The results are given in Table II.

A comparison of the figures show no significant differences between the gall-gladder opacification produced by either of the stereo-isomers in our subjects. It should be noted that faint gall-bladder visualization was occasionally reported by some observers on control films. We conclude that both isomers undergo biliary excretions to a similar extent and that this process is not stereo-specific for iocetamic acid.

We would like to thank our fellow-volunteers for taking part in the study, Dagra Pharmaceuticals and Napp Laboratories Ltd. for providing the stereo-isomers of Cholebrin, Mrs. M. Archer for the radiography and Drs. A. Burridge, K. Hall and P. M. Hacking for grading the films.

Yours, etc.

J. P. OWENS,
M. D. RAWLINS,
M. I. LAVELLE.

Departments of Diagnostic Radiology,
and Pharmacological Sciences (Clinical Pharmacology),
The University of Newcastle upon Tyne.

REFERENCES

JANBROERS, J. M., SANDERS, J. C., TIL, H. P., FERON, V. J., and DE GROOT, A., 1969. Toxicologic and pharmacologic properties of iocetamic acid, a new oral cholecystographic agent. *Toxicology and Applied Pharmacology*, *14*, 232–241.

OWEN, J. P., and LAVELLE, M. I., 1978. Comparative study of iocetamic acid and calcium ipodate in the visualization of the gall-bladder and common bile duct. *Clinical Radiology* (in press).

STANLEY, R. J., MELSON, G. L., CUBILLO, E., and HESKER, A. E., 1974. A comparison of three cholecystographic agents. *Radiology*, *112*, 513–517.

A lightweight breast applicator for setting up tangential fields

THE EDITOR—SIR,

An applicator sold by Atomic Energy of Canada and used by many centres for tangential field irradiation of the breast with ^{60}Co γ rays has a number of shortcomings. Some of these are:

(1) The applicator weighs 11 kg which is too heavy for the staff to handle conveniently.

(2) In order to attach the applicator to the ^{60}Co unit head, staff must physically support the whole weight until it is screwed in at two spots. This is inconvenient and time consuming.

(3) The beam irradiates a Perspex (Lucite) end plate which is in close proximity to the skin. This plate is meant to be a carrier or supporter of bolus material when this is

1978, *British Journal of Radiology*, *51*, 654–655

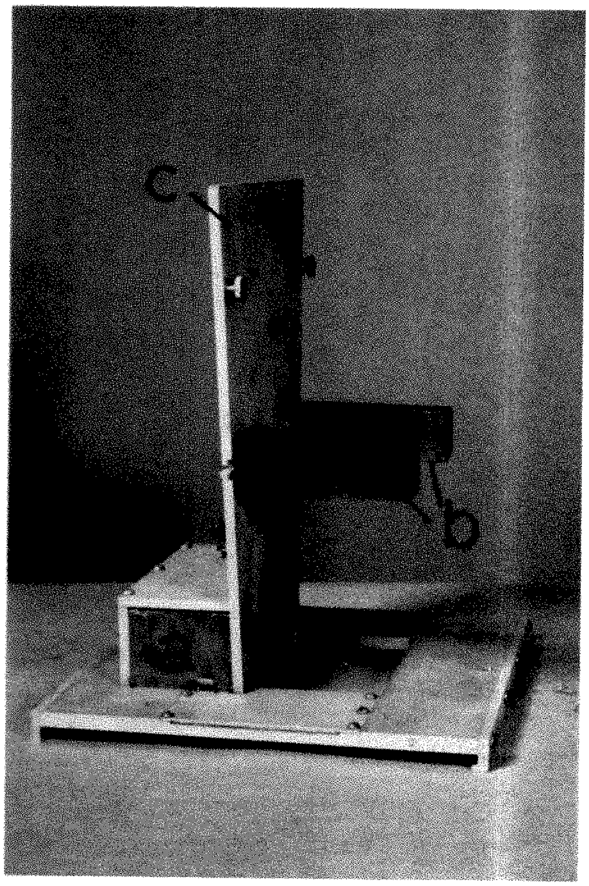


FIG. 1.

(a) Removable shielding lead block. (b) Movable beam trimmers. (c) Detachable distal end 5 cm long.

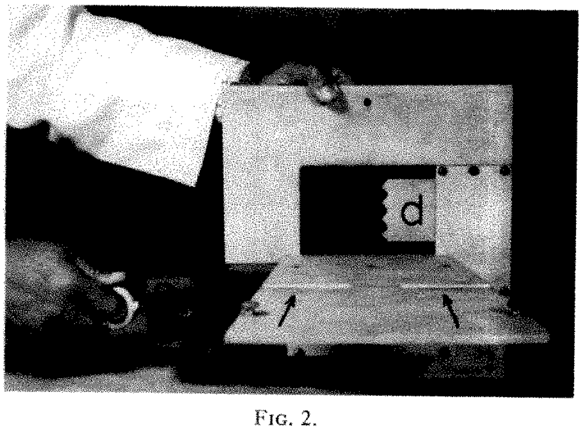


FIG. 2.

Lead shield (a) not completely inserted. Beam trimmers not in place. Arrows show grooves for trimmer. Spring-loaded obturator (d) partially obstructing the path of the beam when the lead shield (a) is not fully inserted.

needed. However, it can cause excessive skin reaction due to secondary electron contamination (Hanson and Grant, 1976).

(4) There are no adjustable beam trimmers on the applicator; therefore it is hard to adjust the field to the marked area to be treated.

(5) The maximum field size is 20 × 10 cm. The width of the field required is often greater than this.

(6) The applicator has a fixed length to keep the SSD at 80 cm. This can cause inconvenience to patients by being in contact with the skin throughout the whole treatment.

In order to eliminate all the above-mentioned undesirable features, an applicator has been designed in our department (Figs. 1 and 2) with the following features:

(1) The applicator weighs 3.4 kg. Most of the weight in the old applicator was due to the lead required for shielding the lower half of the beam which is not used for therapy. In the new applicator this shielding block is detachable and fits like a piston within a sleeve. In order to ensure that the lead shield has been inserted before therapy, a spring-loaded obturator is designed to extend and partially obstruct the field localization light beam if the shielding block is not in place.

(2) The applicator slides in two grooves onto the head of the ^{60}Co unit.

(3) The end of the applicator near the patient is open and has no Lucite plate and therefore no contamination by secondary electrons.

(4) Movable beam trimmers can be attached in about the middle of the applicator.

(5) The field size can be up to 24 × 13 cm.

(6) The distal 5 cm of the applicator is detachable. Therefore, after using the full length for correct SSD the end portion that touches the skin of the patient may be detached in order to avoid patient discomfort.

The applicator* has been tried in our section and proved to be more useful than the old one.

Yours, etc.,
R. ABADIR,
M. EDWARDS.

Radiation Oncology,
University of Missouri Medical Center,
Columbia, Missouri 65201, U.S.A.

REFERENCE

HANSON, W. F., and GRANT, W., 1976. The use of auxiliary collimating devices in the treatment for breast cancer with ^{60}Co teletherapy units. Part II: Dose to the skin. *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *127*, 653–659.

---

*Submitted for patent with the University of Missouri.

Flagyl and radiation-induced chromosome breakage

THE EDITOR—SIR,

Metronidazole ("Flagyl") and similar electron-affinic compounds show great promise as hypoxic-cell sensitizers in radiotherapy. Colony-counting experiments in which the lethal effects of combinations of low LET radiation and Flagyl have been measured (Asquith *et al.*, 1974) have suggested the possible value of this type of compound and initial clinical trials have been started (Urtasun *et al.*, 1977).

Dividing cells which contain unstable chromosome aberrations are unlikely to produce viable cell lines and consequently there is a close correlation between chromosome aberrations and the colony-forming ability of irradiated cells (Dewey *et al.*, 1971; Wolff, 1972). It was decided to examine the influence of Flagyl on the production of chromosome damage and in the present note we report some preliminary

TABLE I

OBSERVED DICENTRIC YIELD PER CELL ±S.E. UNDER VARYING EXPERIMENTAL CONDITIONS

		Control	100 rad	300 rad
Venous	+Flagyl	—	0.11 ±0.023	0.690 ±0.059
	−Flagyl	—	0.107 ±0.008	0.775 ±0.062
Anoxic	+Flagyl	0.000	0.068 ±0.014	0.303 ±0.038
	−Flagyl	0.000	0.021 ±0.006	0.140 ±0.017

observations of the effect of Flagyl on the yield of X-ray induced dicentric aberrations in human lymphocytes from anoxic and normal venous blood.

Samples of anoxic blood (equilibrated with nitrogen containing less than 2 ppm oxygen) and normal venous blood were irradiated with 100 or 300 rad of 250 kV X rays. Lymphocyte cultures were set up for 48 hours according to a routine procedure (Purrott and Lloyd, 1972). The method for producing anoxia in blood will be described elsewhere. Further cultures were set up from blood samples containing 8 mM Flagyl when irradiated under the same conditions. Before incubation, cells from these samples were washed twice in culture medium to remove the Flagyl. At least 200 first metaphase cells from each culture were examined for dicentric aberrations.

The results in Table I show that Flagyl causes a highly significant increase in dicentric yield from irradiated anoxic blood but this increase does not bring the dicentric levels as high as those observed in normal venous blood. No change is observed in the dicentric yield from blood at venous oxygen tension after the addition of Flagyl.

These observations support those of other workers who have measured the influence of Flagyl on reproductive death in normal and malignant tissue (Denekamp and Harris, 1975; Hofer *et al.*, 1977) and illustrate the usefulness of chromosome aberration analysis in the evaluation of radiosensitizers. Further cytogenetic experiments with Flagyl and other radiosensitizers are in progress.

Yours etc
J. S. PROSSER
C. M. WHITE.

National Radiological Protection Board,
Harwell,
Didcot,
Oxon OX11 0RQ.

ACKNOWLEDGMENTS

This work was partly supported by Euratom Contract 171-76-1 BIO-UK. Flagyl was kindly supplied by May and Baker Limited. Mr. M. J. Corp performed the X irradiations.

REFERENCES

ASQUITH, J. C., FOSTER, J. L., and WILLSON, R. L., 1974. Metronidazole ("Flagyl"). A radiosensitizer of hypoxic cells. *British Journal of Radiology*, *47*, 474–481.

DENEKAMP, J. and HARRIS, S. R., 1975. Tests of two electron-affinic radiosensitizers *in vivo* using regrowth of an experimental carcinoma. *Radiation Research*, *61*, 191–203.

DEWEY, W. C., MILLER, H. H., and LEEPER, D. B., 1971. Chromosomal aberrations and mortality of X-irradiated mammalian cells: emphasis on repair. *Proceedings of the National Academy of Sciences, U.S.A.*, *68*, 667–671.

HOFER, K. G., HOFER M. G., IERACITANO, J., and MCLAUGHLIN, W. H., 1977. Radiosensitization of hypoxic tumour cells by simultaneous administration of hyperthermia and nitroimidazoles. *Radiation Research*, *70*, 362–377.

PURROTT, R. J. and LLOYD, D. C., 1972. The study of chromosome aberration yield in human lymphocytes as an indicator of radiation dose. I. Techniques. National Radiological Protection Board, Harwell, NRPB-R2.

URTASUN, R. C., MILLER, J. D. R., FRUNCHAK, V., KOZIOL, D., BAND, P. R., CHAPMAN, J. D., and FELDSTEIN, M. L., 1977. Radiotherapy pilot trials with sensitizers of hypoxic cells: Metronidazole in supratentorial glioblastomas. *British Journal of Radiology*, *50*, 602–603.

WOLFF, S., 1972. In *Frontiers of radiation therapy and oncology*, *6* Ed. by J. M. Vaeth, p. 459 (Basel, Karger).

Book review

Nuclear cardiology: Principles and methods. Edited by Aldo N. Serafini, Albert J. Gilson and William M. Smoak, pp. xv+249, illus., 1977 (Plenum Publishing Corporation, New York), $27.00.

At first glance, this small volume looks suspiciously like a symposium proceedings with nearly 50 authors from half a dozen centres in the U.S.A. However, the editors have, in fact, achieved a much better balanced book than any "Proceedings". Unlike Gaul, it is divided into five parts—fundamentals, shunt detection in congenital heart disease, evaluation of myocardial blood flow and disease, evaluation of ventricular function and radio-immuno assay. The last is only a short note on the assay of blood digitalis whereas the rest of the book is concerned with clinical investigation.

The main four parts include 21 chapters which cover all the main fields of cardiac nuclear investigations. Short introductory chapters in these parts deal rather briefly with anatomy, physiology and pathology. They place the later investigations in context but inevitably lack some detail. The text also places non-isotope investigations in context, though individual chapters vary somewhat from the point of view of critical approach to the pros and cons of the radioisotopic investigations.

The chapters on shunt detection and "first pass" work are good and although much of the book is commendably up-to-date, delays in printing and publication mean that there is little clinical work described with Thallium 201 and also a noticeable lack of work with ECG gateing to study ventricular wall motion.

The index is rather brief. Despite this, the book provides a very useful and fairly comprehensive background to a field of nuclear medicine which is currently of very great interest and it can certainly be recommended.

D. H. KEELING.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1.00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (i.e. April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

World Federation of Nuclear Medicine and Biology

To be held September 17–21, 1978. The Second International Congress of the World Federation of Nuclear Medicine and Biology will provide an international forum for the exchange of scientific information, the dissemination of knowledge, and the world-wide promotion of the discipline of nuclear medicine.

The Scientific Symposia will encompass all the activities and interests of nuclear scientists and physicians: medical and health physics; instrumentation; data analysis; radiochemistry; radioassays; *in vivo* and *in vitro* biochemical and physiological measurements; radiopharmaceuticals; functions and disorders of the cerebral, pulmonary, cardiovascular, abdominal, renal, peripheral vascular, bone, joint endocrine, and metabolic systems.

There will be three pre-meeting courses: cardiovascular nuclear medicine; positrons, cyclotrons, and tomography; nuclear medicine in developing countries. During the meeting, there will be review teaching sessions on the state of the art in clinical nuclear medicine.

The technologist programme will include considerations of quality assurance, recruitment, education and career opportunities.

The meeting has been designed to afford maximum opportunities for exchanges of ideas and views among nuclear colleagues.

Morning activities will provide a plenary session, time for small discussion groups, and for visiting the exhibits of equipment and radiopharmaceutical manufacturers.

Afternoons will be devoted to contributed papers, poster sessions, panels and mini-symposia.

Further information from Dr. H. N. Wagner, President, WFNMB Second International Congress, 1629 K Street, N.W., Suite 700, Washington, D.C., 20006, USA.

Nuclear Medicine in Pediatrics
Joint Meeting with the British Institute of Radiology and the Royal College of Physicians of Edinburgh

A one day meeting on Nuclear Medicine in Pediatrics will be held in Edinburgh on Friday, October 20, 1978.

One session will be devoted to renal disease, one to cardiac and respiratory disease and one to general topics. Dr. David Gilday will be reviewing the clinical application on nuclear medicine in children.

Proffered papers on any aspect of nuclear medicine in paediatrics are invited.

Detailed programme and registration forms available from the General Secretary (September 1978), British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

British Medical Ultrasound Society
Annual Meeting and Exhibition

To be held November 27–28, 1978 at the Civic Centre, Newcastle upon Tyne. Potential exhibitors are invited to contact A. J. Hall, Queen Mothers's Hospital, Glasgow, G3 8SH (041–399 8888 ext. 548).

Papers are invited and authors wishing to submit contributions should send 100–200 word abstract to Mr. A. Whittingham, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne.

Further details from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Workshop on the use of Computerized Tomographic Scanners in Radiotherapy

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

1979 British Institute of Radiology Annual Congress

Will be held at the Middlesex Hospital Medical School, on April 26–27, 1979.

4th Congress of the European Association of Radiology

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

Quantitation of Tumour Response: a Critical Appraisal

The the L. H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Book reviews

Radiology for medical students 595
Atlas of grey scale ultrasonography 598
CRC handbook series in clinical laboratory science. Section A: nuclear medicine, volume 1. 612
Acoustic instrumentation and characterisation of lung tissue 621
Introductory physics of nuclear medicine 621
Abdominal grey scale ultrasonography 627
Pediatric oncologic radiology 627
The handling, storage, use and disposal of unsealed radionuclide in hospitals and medical research establishments (Annals of the ICRP, Vol 1, no. 2 – ICRP Publication 25) 639
Nuclear cardiology: principles and methods 655

Books received

Receipt of the following books is acknowledged as a courtesy to the sender. These publications have been lodged in the Library of The British Institute of Radiology for the use of members.

AREA EXPOSURE PRODUCT METER, I.E.C. Publication 50, 1977, pp.43 (International Electrotechnical Commission, Switzerland), Sw. fr.52.

ANNUAL REPORT 1977, International Agency for Research in Cancer, pp. 173 (World Health Organization, Switzerland), Sw. fr.12.

THE YEAR BOOK OF CANCER, 1977, pp. 499, illus. (YB Medical Publishers Ltd., London), £19·25.

THE YEAR BOOK OF DIAGNOSTIC RADIOLOGY, 1978, pp. 470, illus. (YB Medical Publishers Ltd., London), £22·50.

The British Journal of Radiology (1978)

Supplement No. 14

Reflux and Renal Scarring

by P. G. Ransley. M.A., M.B., F.R.C.S.
and R. A. Risdon, M.D., M.R.C. Path.

Professor C. J. Hodson and his colleagues have shown the essential link in the association of chronic pyelonephritis with vesico-ureteric reflux: renal scarring in the growing kidney is related to intrarenal reflux of urine ("The Pathogenesis of Reflux Nephropathy", British Journal of Radiology Supplement No. 13, 1975). These ideas have now been taken further by Ransley and Risdon, again using the growing kidney of the infant pig. Their starting point is the morphology of the renal papilla. The different shapes of papillae, determined by the lobar structure of the kidney, are critical to the occurrence of intrarenal reflux.

These meticulous experimental studies answer many of the questions which have beset this subject: what are the pressure relationships of intrarenal reflux, why does scarring occur at predictable sites within the kidney, what are the mechanisms of progressive pyelonephritic deformity?

The authors have carried out carefully controlled experiments to test the importance of infection to renal scarring. Does sterile intrarenal reflux alone lead to scarring? Ransley and Risdon show that infection is an essential component to the initiation of the renal scar.

This work has far-reaching practical implications for understanding chronic pyelonephtriis, and therefore for its medical/surgical management. Paediatricians, nephrologists, urologists, radiologists and all who care for children with urinary infection will read it with interest.

PRICE: £3·60 (B.I.R. Members £3·00)

ORDERS TO: Publications, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG

VOL 51 NO 608 AUGUST 1978

The British Journal of Radiology

Contents

Page

Computed tomography in spontaneous intracerebral haematomas. 563
B. E. Kendall and E. W. Radue

The hip joint in Paget's disease (Paget's "coxopathy"). 574
P. B. Guyer and K. C. Dewbury

Renal tubular sludging of meglumine iodipamide (Biligrafin). 579
J. B. Witcombe

The early development of the human skeleton: a radiographic study of fetuses impregnated with silver nitrate. 584
B. J. Cremin, R. M. Fisher and T. J. Hochschild

Pneumatosis intestinalis in children. 589
A. Gupta

Ultrasound and hepatic metastases. 596
F. R. Vicary and I. Shirley

An evaluation of the use of ^{99}Tc^{m}-dimercaptosuccinic acid (DMSA) as a static renal imaging agent. 599
J. B. Bingham and M. N. Maisey

Response of aneurysmal bone cyst to low doses of cobalt 60 gamma radiation with prolonged treatment. 608
V. Shah, N. C. Singhal and J. P. Udawat

Implementation of the Philips treatment planning system for use in radiation teletherapy. 613
R. G. Dale

Mean skeletal dose factors for beta-particle emitters in human bone. Part I: volume-seeking radionuclides. 622
F. W. Spiers, A. H. Beddoe and Joan R. Whitwell

Technical note. 628
Ultrasonic measurement of renal inclination; its importance in measurement of renal length.
P. Farrant and H. B. Meire

Case reports. 631
Solitary non-parasitic hepatic cyst presenting with jaundice.
R. J. Machell and R. Y. Calne
Anterior vascular indentation of the oesophagus.
W. R. Castaneda-Zuniga, K. Amplatz and J. E. Edwards

Short communications. 636
Cytotoxicity and radiosensitization in mouse and man.
Juliana Denekamp
Pitfalls in the use of *in vitro* survival curves for the determination of tumour cell survival with fractionated doses.
L. Zeitz and J. M. McDonald

Proceedings of The British Institute of Radiology. 640
In vivo and *in vitro* radioisotope investigations of diseases involving the endocrine organs (February 16, 1977).
Real-time ultrasound (October 20, 1977).

Proceedings of the British Medical Ultrasound Society (December 7–8, 1977). 644

Correspondence. 653
The biliary excretion of the stereo-isomers of iocetamic acid (Cholebrin).
J. P. Owens, M. D. Rawlins and M. I. Lavelle
A lightweight breast applicator for setting up tangential fields.
R. Abadir and M. Edwards
Flagyl and radiation-induced chromosome breakage.
J. S. Prosser and C. M. White

Forthcoming events. 656

Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0007-1285
12322

October 1978

Acc.
13.x.79

THE BRITISH JOURNAL OF RADIOLOGY

X-ray diagnosis
Radiation oncology
Nuclear medicine
Ultrasound
Radiological physics
Radiobiology
Radiation protection
and related disciplines

Published by
The British Institute of Radiology

The British Journal of Radiology

FOUNDED 1896

The Editorial Committee consists of:

The Editors:

D. K. BEWLEY, M.A., PH.D. F. STARER, F.R.C.P., F.R.C.R.

The Deputy Editors:

B. T. HALE, M.B., CH.B., F.R.C.R., D.M.R.T. N. W. RAMSEY, PH.D., F.INST.P.

J. ROYLANCE, F.R.C.R.

and

The Associate Editors:

A. B. AYERS, M.D., D.M.R.D., F.R.C.R.
THELMA D. BATES, M.B., CH.B., F.R.C.R., D.C.R.A.
D. COSGROVE, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. COTTRALL, B.A., M.SC., PH.D., F.INST.P.
C. D. R. FLOWER, M.A., F.R.C.P.(C), F.R.C.R.
N. E. GILLIES, B.SC., PH.D.
J. A. GLEESON, M.B., F.R.C.P., F.R.C.R., D.M.R.D.
H. GRAVELLE, B.SC., M.B., CH.B., F.R.C.P.(E.), F.R.C.R., D.M.R.D.
J. L. HAYBITTLE, M.A., PH.D.
C. R. HILL, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. KEELING, M.A., M.SC., M.B.
I. KELSEY FRY, D.M., F.R.C.P., F.R.C.R.
B. KENDALL, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. MEIRE, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. PATTON, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. SCOTT, M.D.
T. SHERWOOD, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. VEALL, D.SC., F.INST.P.

The Associate Editors Overseas are:

P. ARMSTRONG, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
J. R. CUNNINGHAM, M.SC., PH.D. (Canada)
H. A. LUKE, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. SIM, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. STANFORD, M.A., F.INST.P. (Australia)

Managing Editor: MRS. LEE SURRY

Communications should be addressed to the Editors in accordance with the Instructions to Authors which are published in the January issue of the Journal in each year and copies of which may be obtained on application to the Managing Editor.

ADVERTISEMENTS: Communications regarding accounts should be addressed to the Institute. All other communications should be addressed to Miss Hilary Cook, Advertising Manager, The British Journal of Radiology, Advertisement Department, 24a Litchfield Street, London WC2H 9NX.

SUBSCRIPTIONS: All communications should be sent to The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England. Notification of change of address should include an old mailing label and the new address. Claims for missing copies can only be allowed if received within three months of publication date.

ANNUAL SUBSCRIPTION: (post free, payable in advance) £40·00 per annum (monthly) (U.S.A. $78). Single copies: £4·00.

Second class postage paid at New York. Mailing agents: N.Y. Expediters of the Printed Word Ltd., 527 Madison Avenue, Suite 1217, New York, N.Y. 10022, U.S.A.

The British Institute of Radiology

Incorporated by Royal Charter
Founded 1897

32 WELBECK STREET, LONDON W1M 7PG
Telephone: 01–935 6237 and 01–935 6867. Cable Address: "Britology, London W.1."

President: W. M. ROSS, T.D., D.L., M.D., F.R.C.S., F.R.C.R.

Hon. Secretaries:

W. HATELY, M.B., CH.B., F.R.C.P.E., F.R.C.R., D.M.R.D. S. B. FIELD, B.SC., PH.D.

Hon. Treasurer: D. T. KERRISK

THE BRITISH INSTITUTE OF RADIOLOGY is an association of persons interested in Radiology and allied subjects. Meetings are held monthly from October until May. Particulars of membership and other information may be obtained on application to the General Secretary at the Institute.

© British Institute of Radiology, 1978

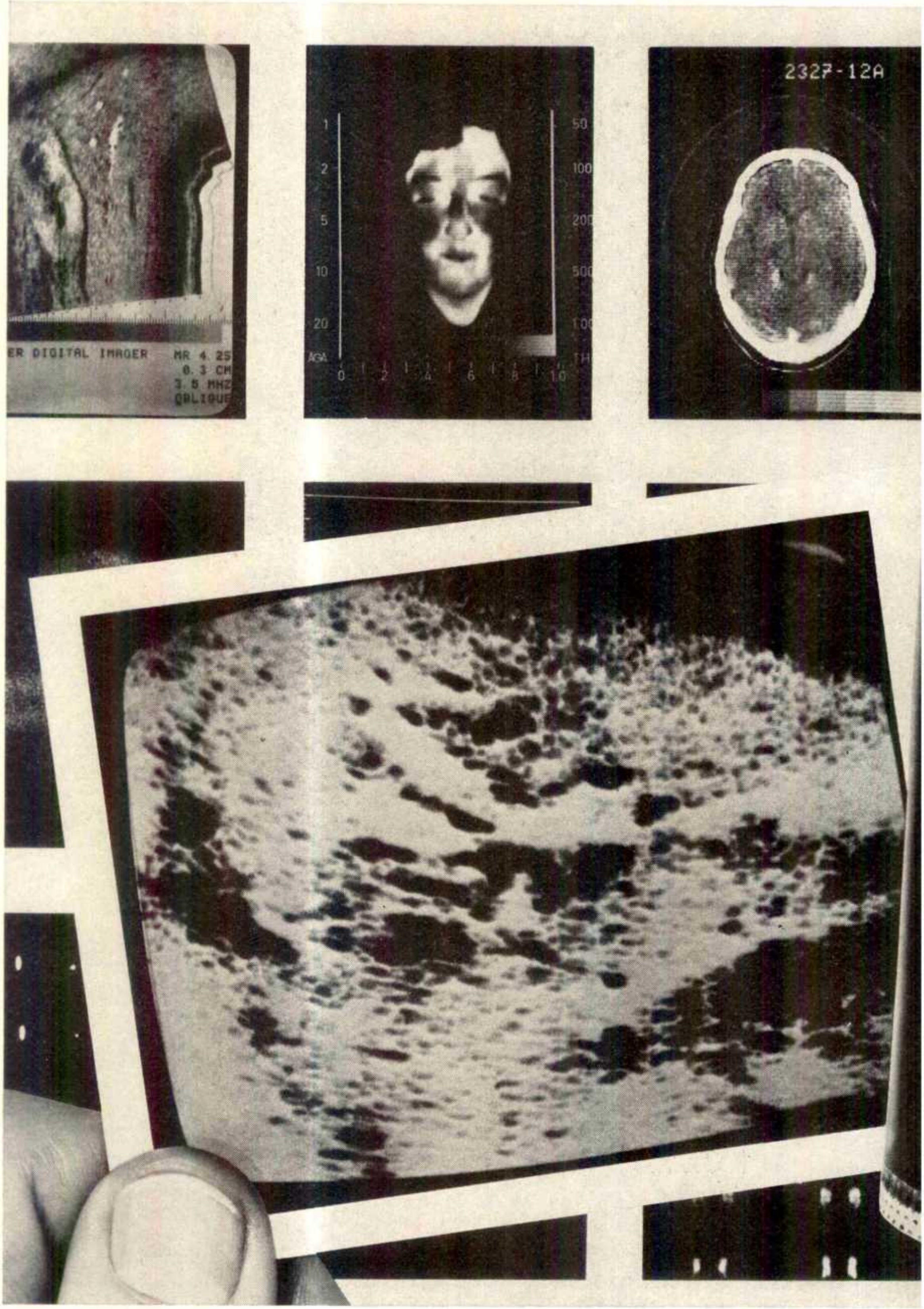
Now there's greater flexibility in the Baritop range.

Baritop G powder is now available in 1kg bags as well as 200g packs, offering you even greater flexibility, to provide barium suspensions of any concentration.

You'll find that it mixes instantly and remains in suspension until required.

Baritop Barium Sulphate available either in suspension, 100% w/v or in powder form for you to mix to the required density.

Concept Pharmaceuticals Limited, Russell House, High Street, Rickmansworth.
Data sheet and additional information available on request.


ER DIGITAL IMAGER
MR 4.25
0.3 CM
3.5 MHZ
OBLIQUE
1
2
5
10
20
AGA
50
100
200
500
100
TH
0 2 4 6 8 10
2327-12A

The diagnostic details. Instantly.

Nothing saves time like Polaroid instant photography.

You can have a fully developed picture for diagnosis from your CRT monitor in seconds.

For sheer convenience, too, there's no better way. You don't need developing and printing equipment. You don't need a darkroom or chemicals. You don't even have to leave the patient. Everything is taken care of by the self-processing film.

Part of our films' convenience is that you know instantly whether the picture you've taken is exactly right for your diagnostic needs. If not, you can retake it on-the-spot while the patient is still in place.

Polaroid self-developing films have the sensitivity, resolution, exposure latitude and grey scale capability to deliver excellent diagnostic photographs.

And one more thing–we offer you more than the speed, convenience and quality of our films. Our Technical Assistance is as close as your telephone. For more information call us on Freefone 2143 or write to Polaroid (UK) Ltd., Business & Professional Products Division, Ashley Road, St. Albans, Herts. AL1 5PR.

Polaroid

Instant films for CRT recording

'Polaroid' is a registered trademark of Polaroid Corporation,
Cambridge, Mass.,USA. Polaroid (UK) Ltd.,
Ashley Road, St. Albans, Herts. © Polaroid Corporation 1978.

Left: Ultrasound Scan. Longitudinal Examination.
Common Bile Duct and Hepatic Ducts. Patient has cancer of the Pancreas. Polaroid Type 667 film. Print size 3¼" x 4¼."

polyfoam®

ANSAFONE SERVICE
operates 5pm-9am and at weekends

unique padding permits passage of X-rays without showing on the plate

RADIOLOGISTS

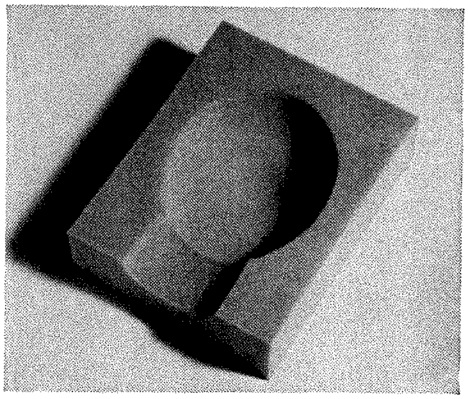
helped to design this Polyfoam position block

ADULT SIZE BLOCK 202, 10″ × 8″ × 3″
CHILD'S SIZE BLOCK 303, 7″ × 6″ × 2″

These blocks as illustrated are cut from a single block of Polyfoam and provide a comfortable non-slip positioning block which lets the patient relax more easily.

POLYFOAM BLOCKS 202 & 303

For more information please write or telephone:



HINDERS-LESLIES LIMITED
Higham Hill Road · London · E17 6EJ
Telephone: 01-531 7172 (10 lines) plus Ansafone

progress
through
research

S&N Member of the SMITH & NEPHEW Group of Companies

CHURCHILL LIVINGSTONE

TO BE PUBLISHED SOON

Atlas of Abdominal Ultrasonography in Children
Gary F. Gates
1978 256 pages approx illustrated £16.50

A clinically oriented atlas organized into sections corresponding to anatomical sub-divisions, this is one of the very few books on ultrasonography which are directed exclusively to childhood disease.

AVAILABLE NOW

Atlas of Gray Scale Ultrasonography
Kenneth J. W. Taylor
1978 426 pages 469 half-tones + 584 line drawings £19.50

A unique book providing a basic reference to all normal and abnormal ultrasound appearances. The scans are of outstanding quality, with line drawings illustrating the main anatomical features of each scan.

Cardiac Catheterization and Angiocardiography
David Verel and Ronald C. Grainger
1978 Third edition 192 pages 64 pages of plates £13.00

This book will enable trainee cardiologists to gain knowledge of the radiological aspects of angiocardiography and radiologists to develop experience of cardiac investigation.

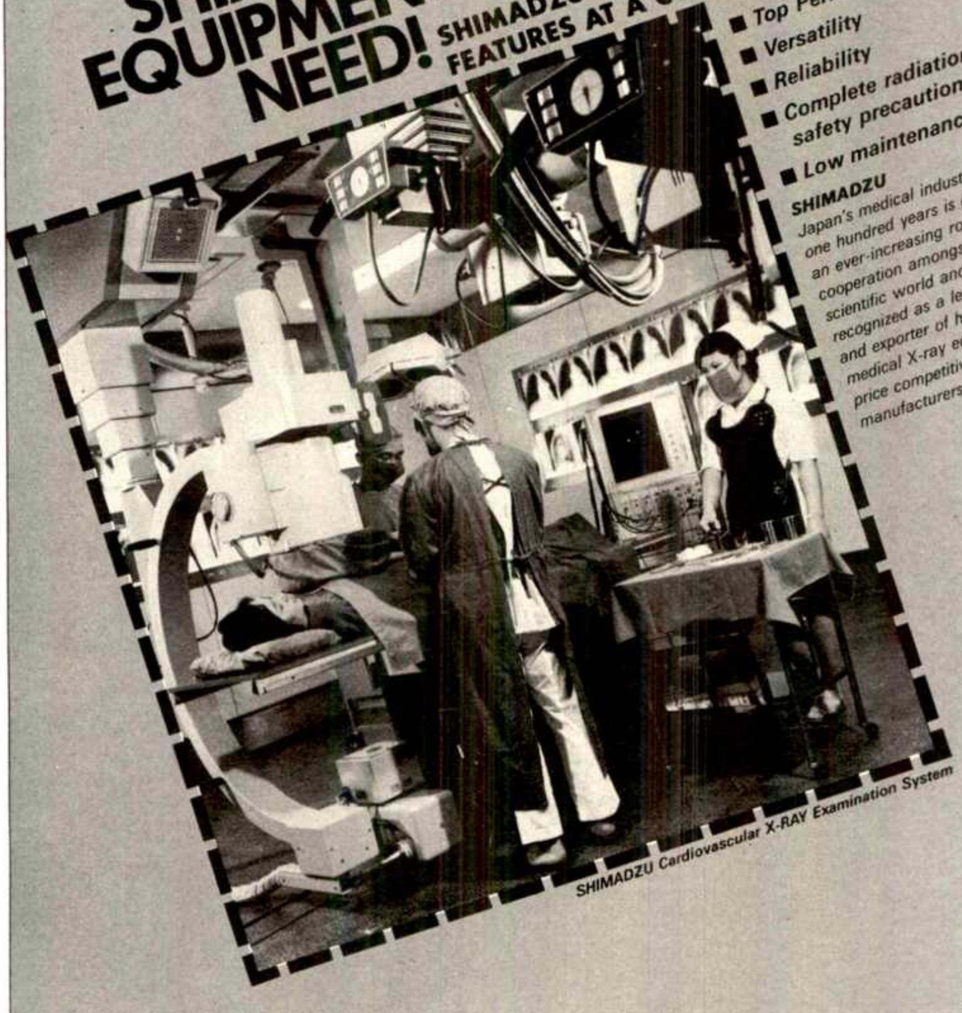
Churchill Livingstone 23 Ravelston Terrace Edinburgh EH4 3TL

A ROOM FULL OF SHIMADZU X-RAY EQUIPMENT IS ALL YOU NEED!

SHIMADZU X-RAY EQUIPMENT OFFERS ALL THESE FEATURES AT A COMPETITIVE PRICE

- Top Performance
- Versatility
- Reliability
- Complete radiation safety precautions
- Low maintenance cost

SHIMADZU
Japan's medical industry pioneer for one hundred years is continuing to play an ever-increasing role in international cooperation amongst the leaders of the scientific world and is internationally recognized as a leading manufacturer and exporter of highly sophisticated medical X-ray equipment at a price competitive with all leading manufacturers.



SHIMADZU Cardiovascular X-RAY Examination System

SHIMADZU
SEISAKUSHO LTD. KYOTO JAPAN
INTERNATIONAL MARKETING DIV.
14-5, Uchikanda 1-chome Chiyoda-ku, Tokyo Japan Phone: Tokyo 03-296-2352
Overseas Telex: No.0222-4275 SHMDT J Cable Address: SHIMADZU TOKYO

SHIMADZU MID-EAST SCIENTIFIC OFFICE
Flat No. 10, 16 Mahmud Azmi Street Zamalek. Cairo
Arab Republic of Egypt(P.O. Box: Zamalek P.O. Box 32, Cairo)
Phone: 804375 Cable Address: MIDSHIMAZU, CAIRO

AUSTRALIA
THE NORTH BRISBANE HOSPITALS BOARD ADMINISTERING THE ROYAL BRISBANE HOSPITALS GROUP AND ASSOCIATED HOSPITALS
DIRECTOR OF DIAGNOSTIC RADIOLOGY

Applications are invited from specialist radiologists for appointment to the position of Director of Diagnostic Radiology, The North Brisbane Hospitals Board.

The North Brisbane Hospitals Board controls the Royal Brisbane, Royal Women's and Royal Children's Hospitals and these are major teaching hospitals for the University of Queensland. The Royal Brisbane Hospital provides medical, surgical, outpatient, gynaecological, radiotherapy, casualty, orthopaedic and psychiatric services, with approximately 1,400 beds; The Royal Children's Hospital paediatric treatment with approximately 200 beds and the Royal Women's Hospital obstetric and neonatal care with approximately 350 beds. The day-to-day running of the complex is in the hands of a Hospital Executive comprising three Executive Directors—Medical Services, Nursing Services and Administrative and Support Services.

Each hospital in turn has a Management Committee comprising the three Branch Heads within that hospital responsible to the Hospital Executive administratively, with each Branch Head having functional responsibility to the appropriate Executive Director.

The Director of Diagnostic Radiology will be responsible to the Executive Director, Medical Services for the radiological services of the Board's Hospitals as a whole and to the Medical Superintendents of the individual hospitals for radiological services within those hospitals.

The University of Queensland has indicated that it will give sympathetic consideration to a request that the Director of Radiology be given formal honorary status in a University Department.

The appointment will be permanent after a twelve month probationary period, in accordance with the terms of appointment.

The appointee will be entitled to 5 weeks annual leave, sick leave, conference leave, and overseas study leave (usually taken at the end of seven years) but by special arrangement with the Board after a shorter period.

The position is full time and superannuated. Salary is $36,763 per annum and is currently under review.

Information on Queensland as a whole and Brisbane in particular may be obtained from the Agent General for Queensland, 392 and 393 Strand, London.

Further particulars may be obtained from the Executive Director of Medical Services. Applications giving full details of qualifications, age and experience, together with the names and addresses of three referees should be forwarded to the Executive Director of Medical Services, Dr. Peter Grant, The North Brisbane Hospitals Board, Base Hospitals Post Office, Brisbane 4029, Australia not later than 31st December, 1978. (6947)

The HADASSAH MEDICAL ORGANIZATION

invites applications for the post of

HEAD OF DEPARTMENT OF DIAGNOSTIC RADIOLOGY

at the Hadassah University Hospital, Ein Kerem, Jerusalem.

We are seeking a candidate with rich clinical experience, background in undergraduate and graduate teaching, and research, and with proved administrative ability.

The post is linked with high academic status in the Hebrew University-Hadassah Medical School.

Applications and enquiries, accompanied by curriculum vitae and list of publications, may be addressed to the **Director General, Hadassah Medical Organization, Kiryat Hadassah, Jerusalem, Israel, until November 30, 1978.**

WANTED: A

RADIOTHERAPIST

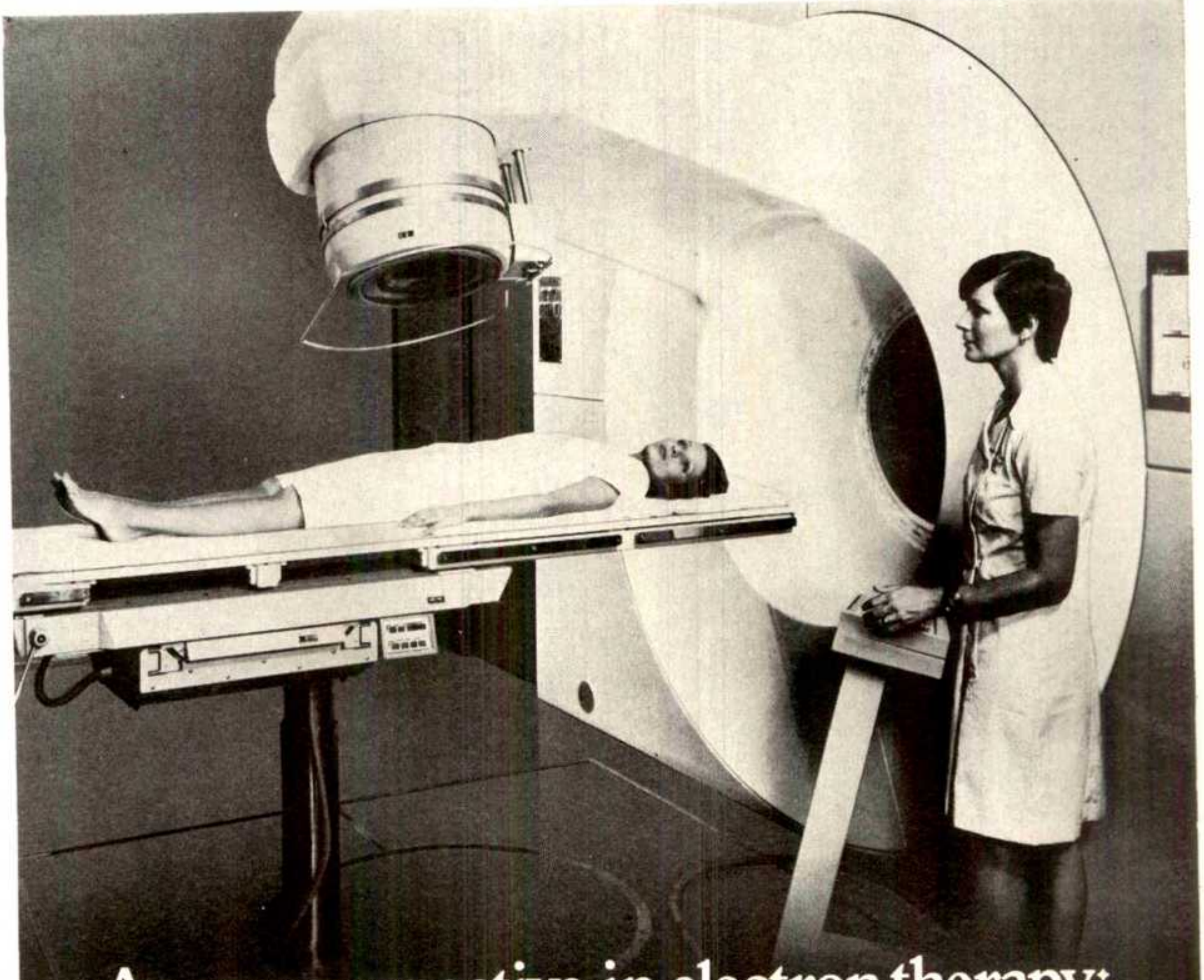
for a Catholic Cancer Hospital in Malaysia. Must be registerable in Malaysia and with the DMRT or FRCR.

Terms negotiable. 5 years experience in speciality. Application giving dates of qualification, age, experience and names of three referees.

Equipment: 1 Cobalt teletherapy unit (K.I.V. 2 Teletherapy units). Radium.

Applications to:

The Hospital Superintendent,
Mount Miriam Hospital,
Jalan Bulan,
Fettes Park,
Penang,
West Malaysia.



A new perspective in electron therapy: the SL 75-14

As the first company to introduce practical linear accelerators operating in electron energy ranges up to 20 MeV, Philips have opened up new perspectives in radiation therapy. Experience has now shown that electrons in the 14 MeV range, together with 10 MV X-rays, provide the best results in the vast majority of modern applications.

With the SL 75-14, a new addition to the Philips range, high-energy electron therapy is no longer confined to a few highly specialized clinics. Sharing the high standards of mechanical and electronic engineering which characterize the SL 75 range, the SL 75-14 is a compact linear accelerator offering electron energies from 4 to 14 MeV, with rapid changeover to 10 MV X-rays.

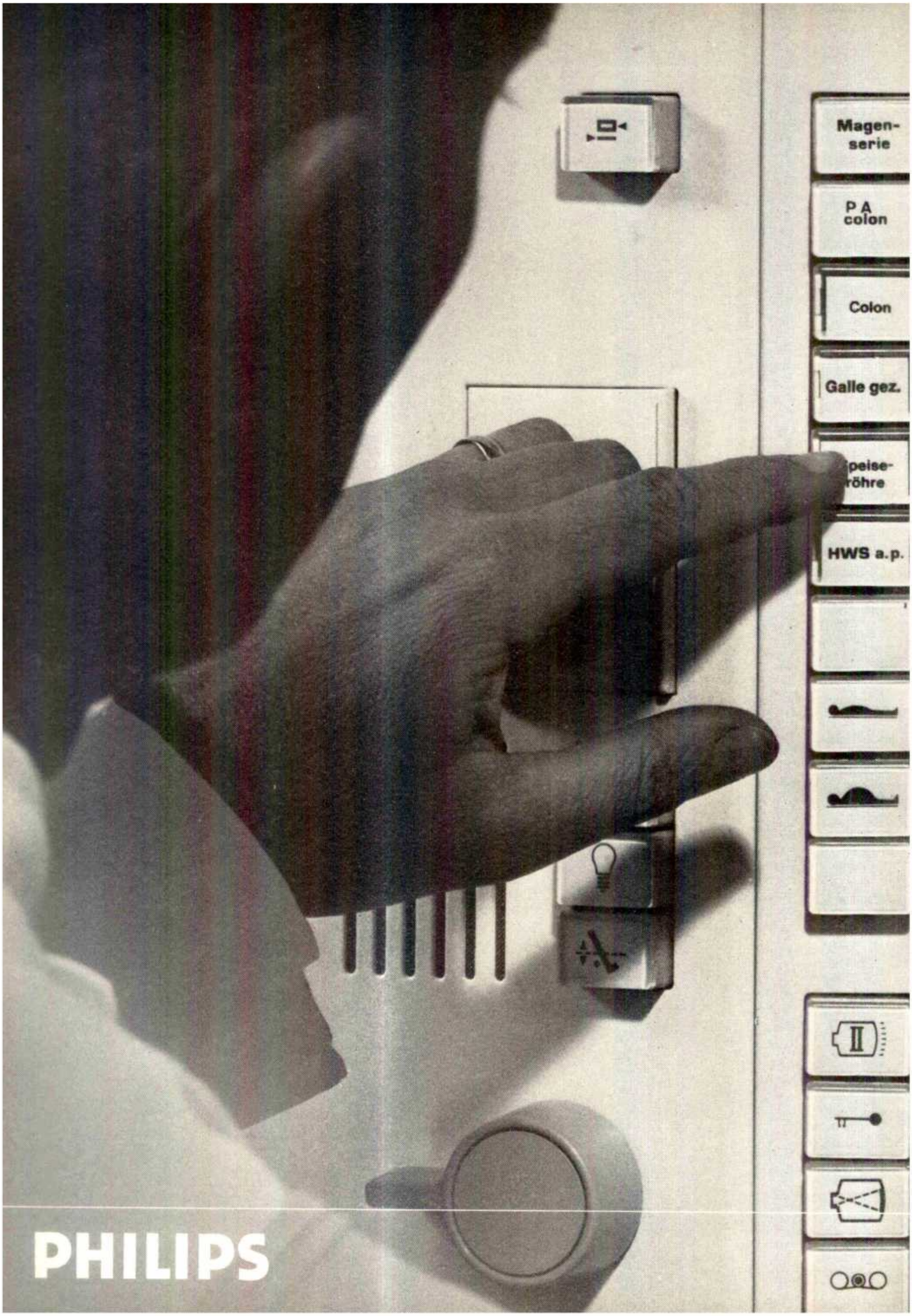
Designed - and built - for years of trouble-free service, the SL 75-14 is a sound economic investment for the busy therapy department, enabling the therapy staff to work at maximum efficiency with minimum stress.

NV Philips' Gloeilampenfabrieken
PCP/Medical Systems Division
Building QM, Eindhoven, The Netherlands

Philips Medical Systems Ltd.
45 Nightingale Lane Balham,
London SW 12 8SX

PHILIPS

PHILIPS Medical Systems


Magen-serie
P A colon
Colon
Galle gez.
Speise-röhre
HWS a.p.
PHILIPS

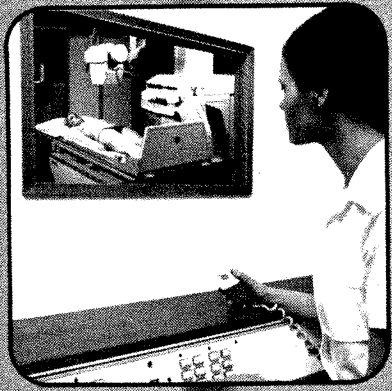
No need to shout for kVs. Modular means they're right at your fingertips.

The Philips modular generator series gives you full control of your generator while attending to the patient being examined. Controls for the modular generator are integrated in the serial changer of the DIAGNOST 73, within your natural reach so that you can select the appropriate parameters for every routine examination yourself. This system of anatomically programmed radiography leaves you free to concentrate on the patient, while retaining full control over the generator.
The modular construction allows the installation to be designed to meet your specific requirements, and to be extended as your department grows.

Modular means made to measure.

All parameters you have chosen on the serial changer are indicated on the generator desk.

For bucky work on the DIAGNOST 73, or an additional unit, the generator desk incorporates additional controls for anatomically programmed radiography. You are free to distribute the settings you require over the available push-buttons in whatever way you like.



The generators incorporate automatic kV and mA control ensuring bright, evenly illuminated fluoroscopy pictures. Moreover, the dual programme technique enables you to change instantly to full size.

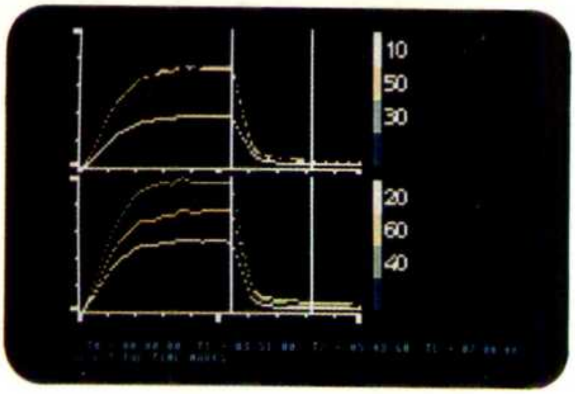
For detailed information, write to: Philips Medical Systems,
Eindhoven, The Netherlands
or Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8 SX.

PHILIPS

Medical Systems

Conclusive evidence

78-01-02 LUNGVENTILATION DORSAL, 125 XE, TRANSIT TIME
0 -100% M=54 N=31094 T=01:00.00

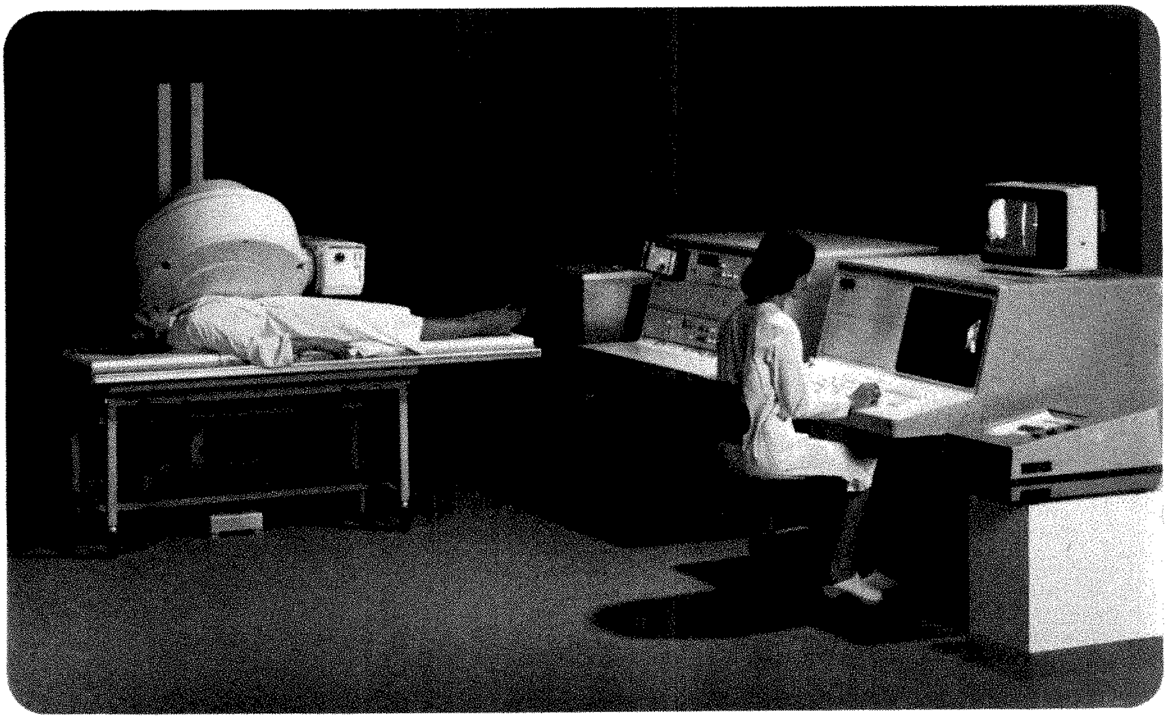


PHILIPS Medical Systems

The Philips Large Field Gamma Camera, with its full 38 cm field of view, provides high-resolution images with excellent homogeneity. The dorsal view of two lungs on a single image, shown in black and white on the left, is a typical example.

The colour image and curves, forming part of a lung ventilation study, have been obtained using the Philips Processing and Display System. This system offers a full range of programs for functional dynamic studies such as those of the heart, kidneys, lungs and brain. The programs, proved in clinical practice, are fast and easy to use, offering a wealth of diagnostic information.

Together, the Large Field Gamma Camera and the Processing and Display System provide conclusive evidence in doubtful cases.



The **Large Field Gamma Camera,** with its **full** 38 cm field of view, offers superb imaging facilities.
The imaging system, based on the Anger principle, consists of 37 bialkali detectors arranged on a single 48 cm diameter crystal. Resolution and homogeneity are excellent, and high count rates can be accepted without significant distortion. Features of the Large Field Gamma Camera include:

- high resolution with excellent homogeneity (3 mm intrinsic lead bar resolution)
- high count rate (100 K counts/s), ^{99m}Tc, 20% window
- fast, easy operation
- extremely stable electronics
- separate scopes for positioning and recording
- full range of ancillary equipment

The **Processing and Display System** provides a wide choice of data acquisition and processing programs for static and dynamic studies. Its functions include quantitative and qualitative analysis, correction of image information, enhancement of selected spatial frequencies, and functional scanning. The results are displayed as enhanced images, time/count histograms, and alphanumerical information including analysis functions and lists of patients.
Data processing and data acquisition, even from several cameras, can take place simultaneously, allowing a large work load to be handled.

In addition to the Large Field Gamma Camera and the Processing and Display System, Philips offer a **Normal Field Gamma Camera** with a 26 cm field of view, as well as a complete range of peripherals.
Multi Formatter. For direct recording of static, dynamic, whole body and gated studies on standard X-ray film.
Total Body Scan Unit. For large-area scanning in combination with the Multi Formatter. **Spectrum Analyser.** For display of the radio-isotope spectrum, and window settings.

Part of a complete program of nuclear medicine equipment and systems, and fully supported by an international service organization, the Philips Large Field Gamma Camera and Processing and Display System combine operational simplicity and efficiency with applicational flexibility and reliability.

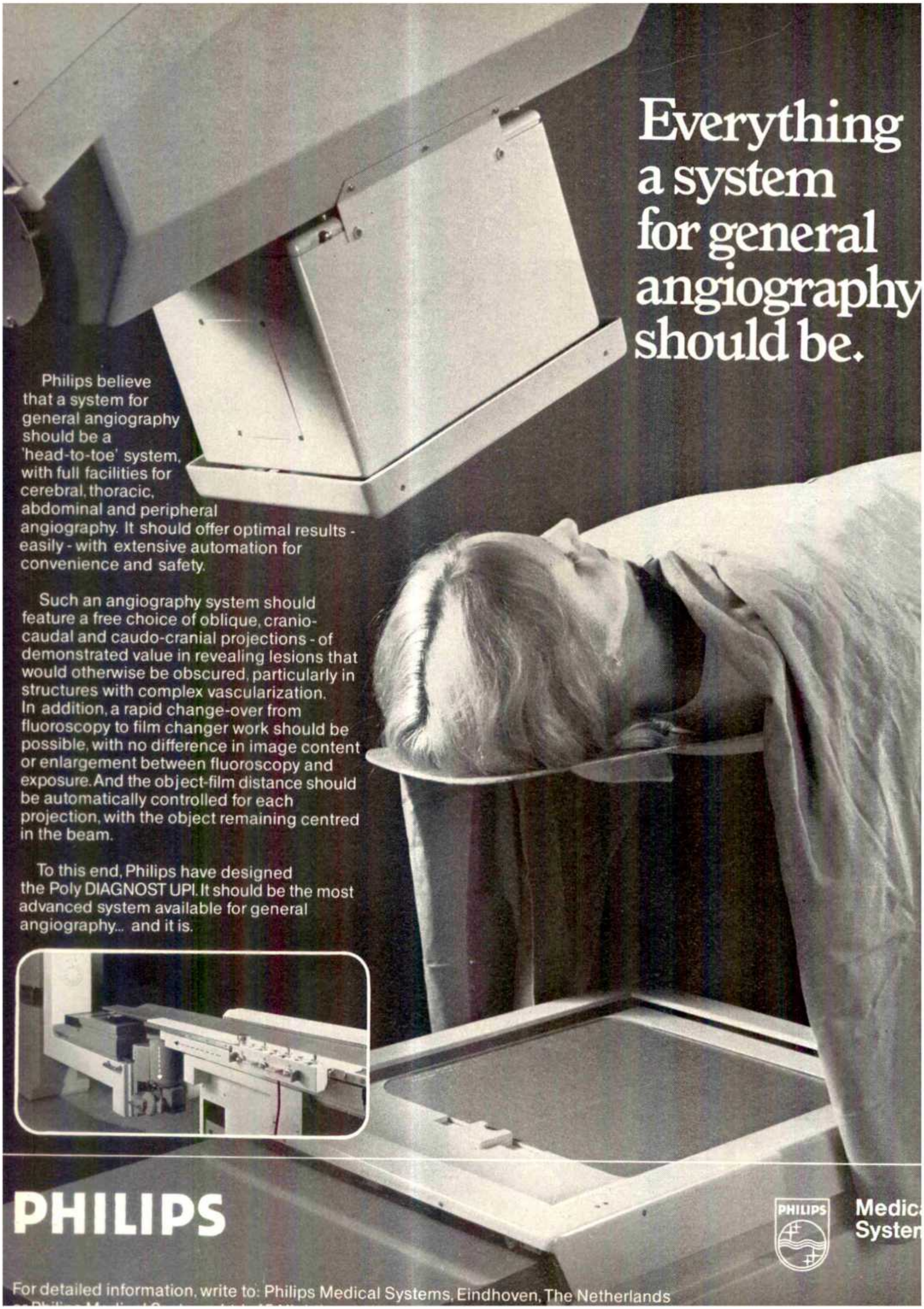
COUPON

If you would like further evidence on our nuclear medicine program, complete this coupon and send it to: Philips Industries, Medical Systems Division, Building QM, Room 347, Eindhoven, the Netherlands

Institution: ....
Name/Position: ....
City/Country: ....
Street/P.O. Box: ....

PHILIPS

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd.
45 Nightingale Lane London SW12 8SX



Everything a system for general angiography should be.

Philips believe that a system for general angiography should be a 'head-to-toe' system, with full facilities for cerebral, thoracic, abdominal and peripheral angiography. It should offer optimal results - easily - with extensive automation for convenience and safety.

Such an angiography system should feature a free choice of oblique, cranio-caudal and caudo-cranial projections - of demonstrated value in revealing lesions that would otherwise be obscured, particularly in structures with complex vascularization. In addition, a rapid change-over from fluoroscopy to film changer work should be possible, with no difference in image content or enlargement between fluoroscopy and exposure. And the object-film distance should be automatically controlled for each projection, with the object remaining centred in the beam.

To this end, Philips have designed the Poly DIAGNOST UPI. It should be the most advanced system available for general angiography... and it is.

PHILIPS

Medic
Syste

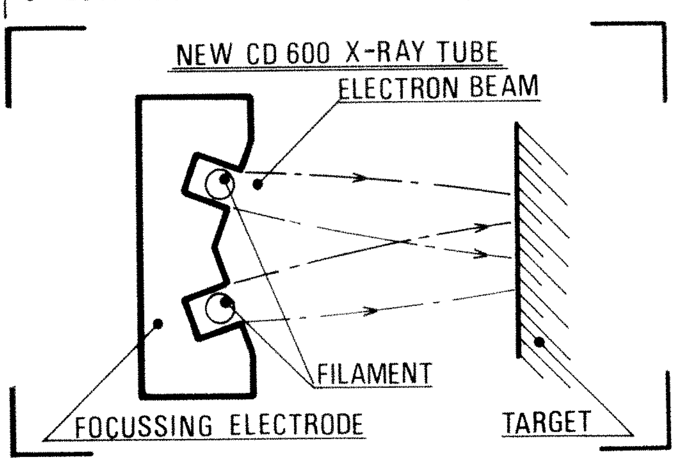
For detailed information, write to: Philips Medical Systems, Eindhoven, The Netherlands

NEW second generation

600 m A p

Capacitor Discharge Mobile

- SUPER OUTPUT 600 mAp/125 kVp
- MILLISECOND SWITCHING 2–60 mAs in 15 steps
- IMPROVED MANOEUVRABILITY three forward speeds and two reverse – extra low speed for bedside adjustment
- UNIQUE HIGH POWER CD600 X-RAY TUBE fine focus, high capacity
- LOW COST half cost of cordless systems

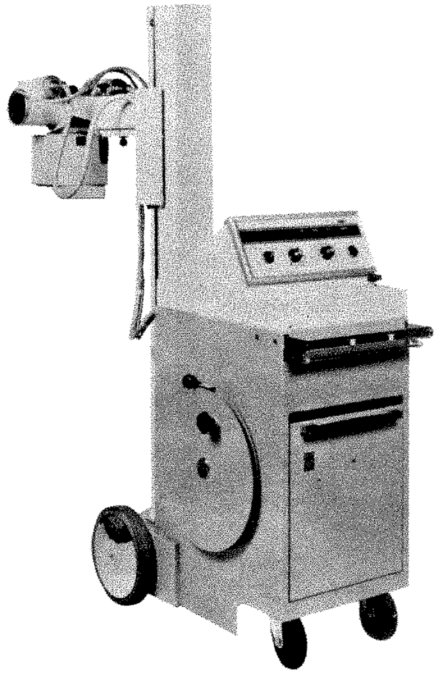


The second generation series CD600 capacitor discharge X-ray tubes have been designed on a new principle using a focussing electrode to cut-off the tube current in place of the grid which was previously used.

With this tube, two 0·8 mm focal spots are superimposed on the target slightly shifted from each other. This results in a high power peak intensity distribution over a focal spot effective size 1·2×1·2 mm.

A great improvement is achieved in the Modulation Transfer Function over the conventional tube and therefore excellent detail at high tube mA loadings is achieved.

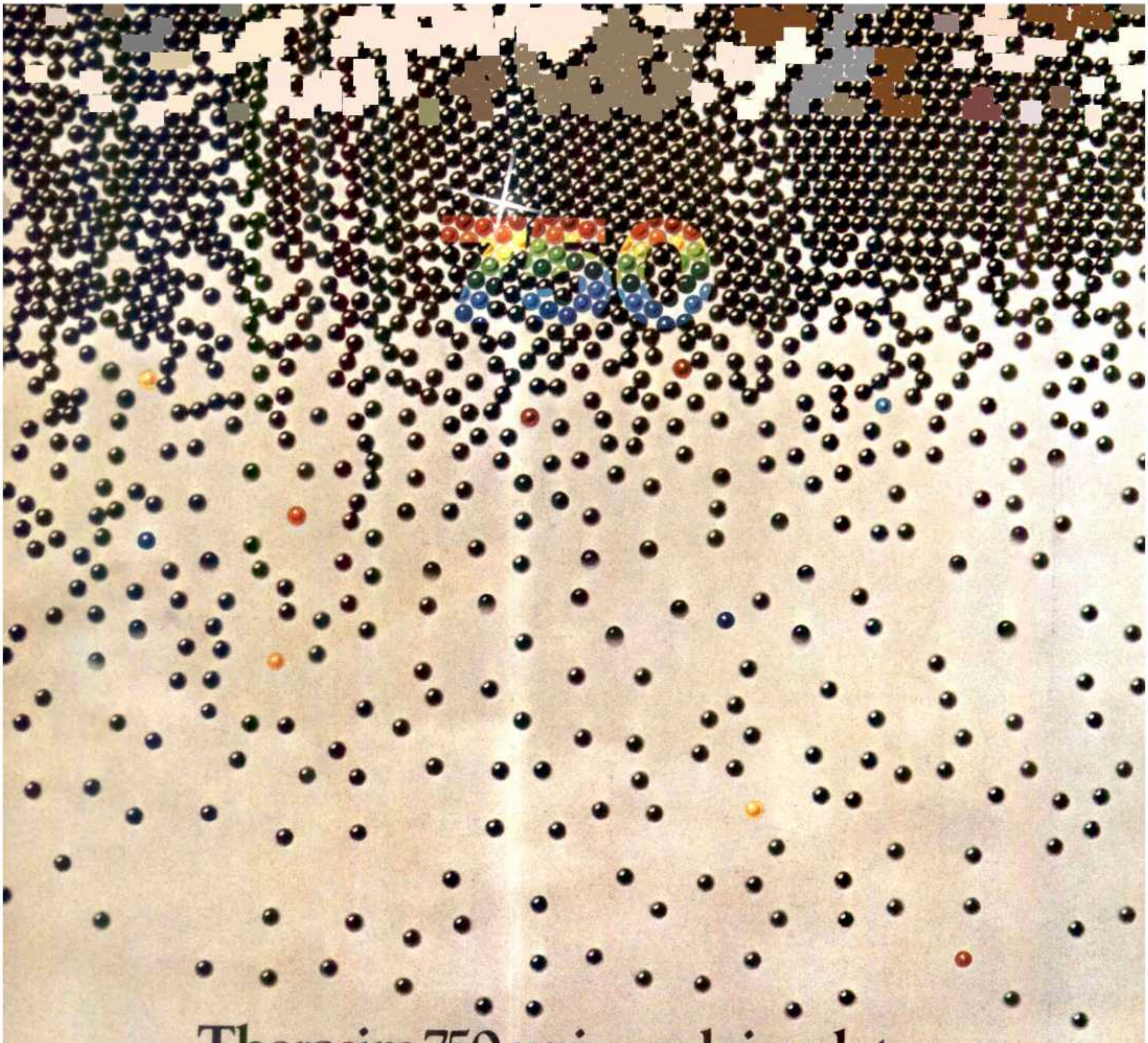
The use of this double focus combination also reduces individual filament temperature and provides longer tube filament life than conventional tube design.

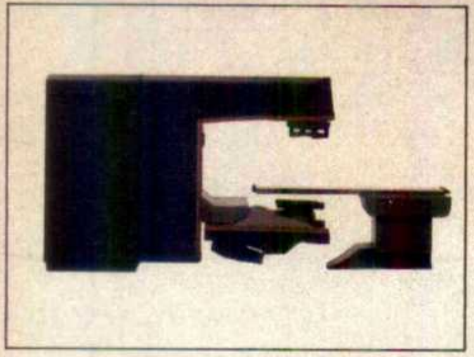


Before making any decisions, contact us and arrange a demonstration in your own Department.

TODD RESEARCH LTD
ROBJOHNS ROAD
CHELMSFORD CMI 3DP
TEL. (0245) 62233/7 TELEX 99327

*Our 1978–9 catalogue is now available. Contact us and a copy will be mailed by return.





Therasim 750 universal simulator. Adding dimensions to treatment planning.

From AECL comes the most advanced teletherapy treatment simulator available — Therasim 750. It brings to treatment planning a degree of accuracy as yet unmatched by conventional methods while significantly increasing the scope of the terms universality, convenience, reliability, and efficiency.

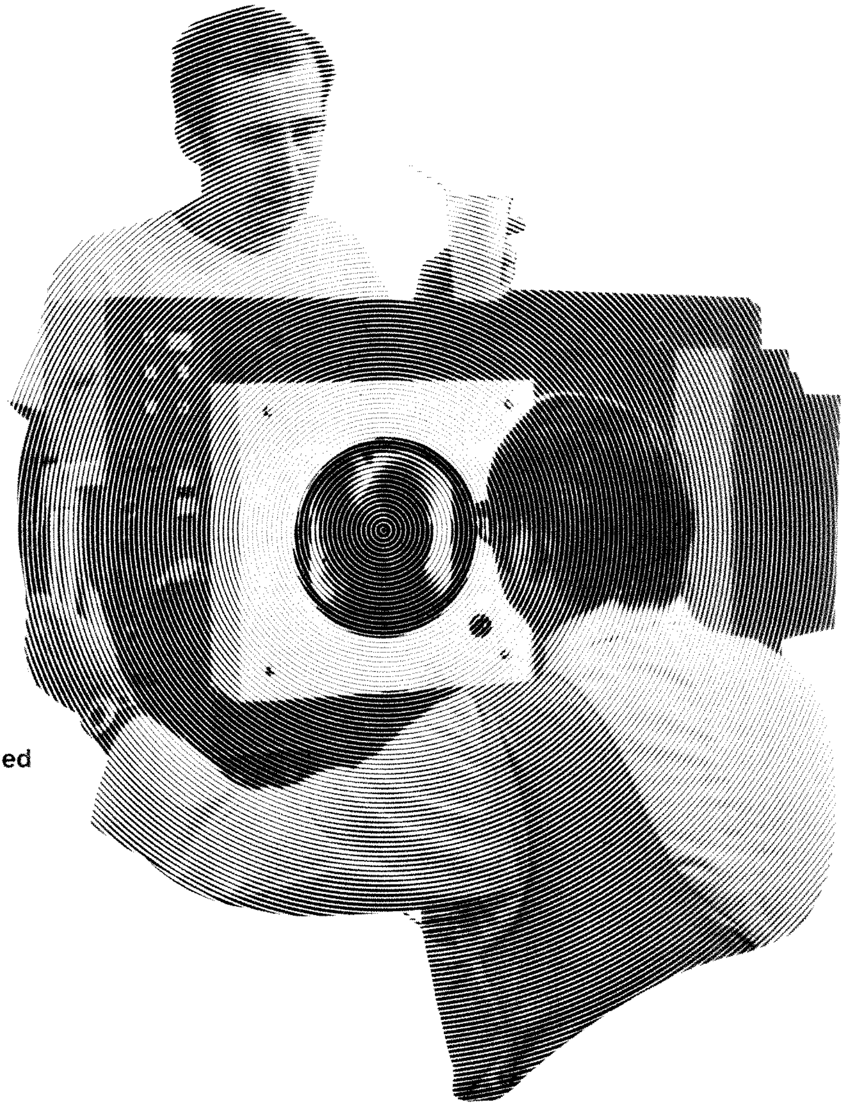
Therasim 750 provides the widest possible range of simulation characteristics for rotation treatment units of all types and under the most demanding of conditions. Now, with the Therasim 750 Universal Simulator, your treatment planning can equal the sophistication and effectiveness of the treatment units themselves.

For further information on how you can add dimensions to your treatment planning, contact AECL.

Atomic Energy of Canada Limited
Commercial Products

P.O. Box 6300, Ottawa, Canada K2A 3W3. Tel.: (613) 592-2790. Cable Nemota. Telex: 053-4162.
In the United States: Chicago: (312) 593-3242. Philadelphia: (215) 441-5353. Atlanta: (404) 987-9280. Dallas: (214) 233-0939. Los Angeles: (714) 989-3900
In Australia: P.O. Box 57 Crow's Nest North Sydney 2065 NSW.

40 years of experience and expert knowledge can be made yours very easily



Oldelft

Oldelft England ltd.
16 Barclay Road, Croydon CRO 1 JN
Tel. (01)681 1171, telex 946154

Odelscope: image-intensifier-improved fluoroscopy

Adding the Odelscope to your fluoroscopic device is combining fluoroscopic screen convenience with the benefits of image intensification in a simple and effective way. The excellent image definition, the low lag, the wide-angle screen and the easy compatibility of the Odelscope with practically all fluoroscopic tables give a new dimension to fluoroscopy.

Radiodiagnosis
Odelca x-ray cameras
100 mm System for spotfilm photography
Deltorax chest film changer
Odelscope image intensifier for fluoroscopy

Ultrasound
Real time linear phased array systems
Cardiac phased array sector scanners
General purpose gray-scale compound scanners

Nuclear medicine
Gamma cameras with complete range of accessories (e.g. multi-imager, whole body scanning bed)

Radiotherapy
4 and 15 MeV linear accelerators
Cobalt units

Radiotherapy planning
Simulix-Y simulator with Simtomix accessory for analog whole body tomography

Pulmonary function testing
Computerized equipment for the pulmonary lab
Automated procedures in spirometry, flow/volume loop analysis and exercise testing

---

Head Office: Holland, (nv Optische Industrie De Oude Delft) 2612 xe Delft, Postbox 72, Tel. (015) 13 29 23 - 12 40 44. Telex 32 364.
België/Belgique 2100 Deurne, Twee Gezusterslaan 34.
Tel. (031) 24 93 05.

Deutschland D 6300 Giessen/Lahn, Postfach 5420.
Tel. (0641) 4 10 49.
España Madrid 16, Uruguay 13. Tel. (01) 259 1698
France 91400 Orsay, B.P. 86. Tel. (01) 907 5900
Italia 00146 Roma, Via della Vasca Navale 84. Tel. (06) 55 84 311.

Japan Osaka, Postbox 1042. Tel. (06) 309 09 61
Sverige 17206 Sundbyberg 6, Postbox 670, Tel. (08) 98 38 95.
Schweiz 8618 Oetwil am See, Zelglistrasse 5. Tel. (01) 92 91 318.
USA Fairfax, Virginia 22030, 2735 Dorr Avenue,
Tel. (703) 573 7020

Pitman Medical

A User's Guide to Diagnostic Ultrasound

I M Shirley, R J Blackwell, G Cusick, D J Farman, F R Vicary

This is an essentially practical guide for the newcomer to the subject. It familiarises the reader with the essential physical principles and limitations of the technique. These must be thoroughly understood if the technique is to be used to its best effect and errors of interpretation are to be avoided. These physical principles are presented in such a way that they will be easily understood by medical readers. To this end, the physics is kept to a descriptive level and often illustrated with examples drawn from clinical investigations and problems.

340 pages Illustrated Cased £12·00 net

Ultrasound in Tumour Diagnosis

C R Hill, V R McCready, D O Cosgrove

The past few years have seen rapid development in the quality of commercially available medical ultrasonic imaging techniques, with their consequent application to a wide range of new diagnostic problems. In the area of tumour diagnosis modern techniques have the potential to detect some of the soft tissue pathologies, often small in scale and subtle in nature, that are commonly associated with malignant change but are undetectable by other techniques. This volume brings together the experience of leading clinicians and researchers in various aspects of the subject and provides a systematic account of the scope of ultrasonic methods for dealing with a range of particular problems that arise in the identification and management of malignant disease.

256 pages Illustrated Cased £11·00 net

Clinical Ultrasound of the Breast

T Kobayashi

Diagnostic ultrasound was first applied to the differential diagnosis of breast cancer in 1952. Since that time many technological advances have been achieved especially with regard to the refinement of displayed images. These have reached an important stage in clinical application and offer more refined diagnostic information for breast cancer. This atlas shows the present status of echographic diagnosis of breast cancer in pictorial fashion and the text is kept to an absolute minimum. The illustrations consist of pictures recorded by the sensitivity graded method using bistable technique in the first section, grey scale imaging in the second edition and finally, target expansion technique for detection of early breast cancer.

170 pages Illustrated Cased £16·00 net

To your Bookseller OR Pitman Medical, 57 High Street, Tunbridge Wells, Kent TN1 1XH

Please send me:

		Tick
A User's Guide to Diagnostic Ultrasound	£12·00	☐
Ultrasound in Tumour Diagnosis	£11·00	☐
Clinical Ultrasound of the Breast	£16·00	☐

(Please add 50p per copy for postage and packing)

I enclose my cheque for £........ OR

Debit my Access/Barclaycard with amount due

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Name ....

Address ....

....

Signature ....

AGFA-GEVAERT

Contrast, definition, brilliance - in a word, CURIX

Enquiries have proved that most radiologists working with Curix RP1 film prefer the material because of its outstanding qualities.

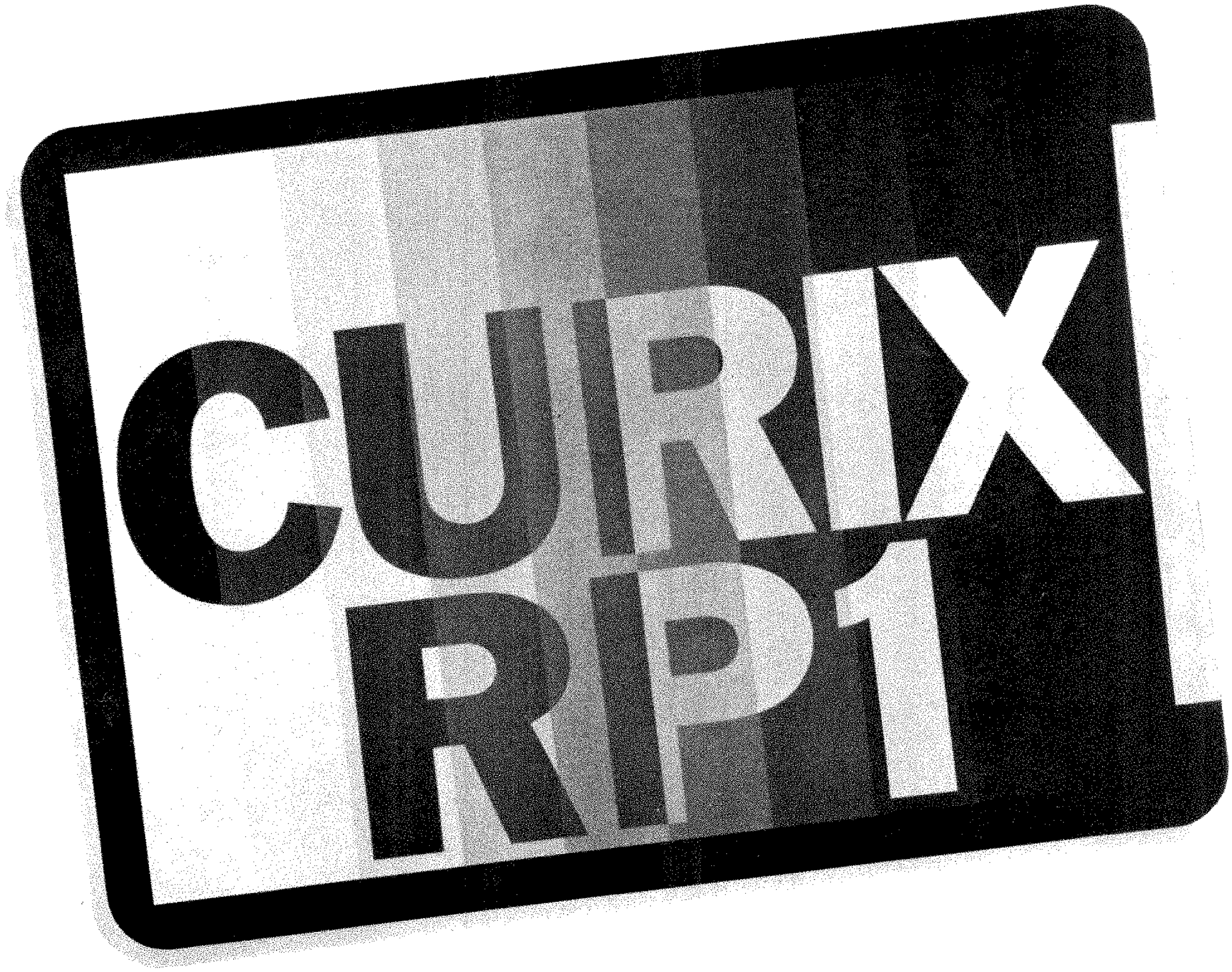
In making their choice, low fog level, contrast, image sharpness and sensitivity were of prime importance. In a word, they required "quality". Curix offers that quality.

The film combines all the desired properties which give the radiologist more detailed information on which to base a safe, sure diagnosis.

It's easy to see why Curix is our biggest selling X-Ray film.

Isn't it time you proved the brilliance of Curix RP1.

Further information from:
Agfa-Gevaert Ltd.,
Medical X-Ray Sales Dept.,
27 Great West Road, Brentford,
Middlesex TW8 9AX.
Tel: 01-560 2131

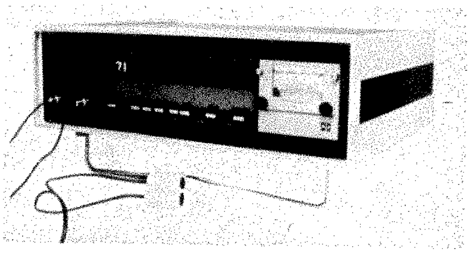


DIGITAL ECHO ENCEPHALOGRAPHS

(MANUFACTURED BY RADIONICS MEDICAL DIVISION OF CANADA)

digiecho 1000

- portable, battery operated
- requires no previous experience
- digital measurement of midline
- competitively priced

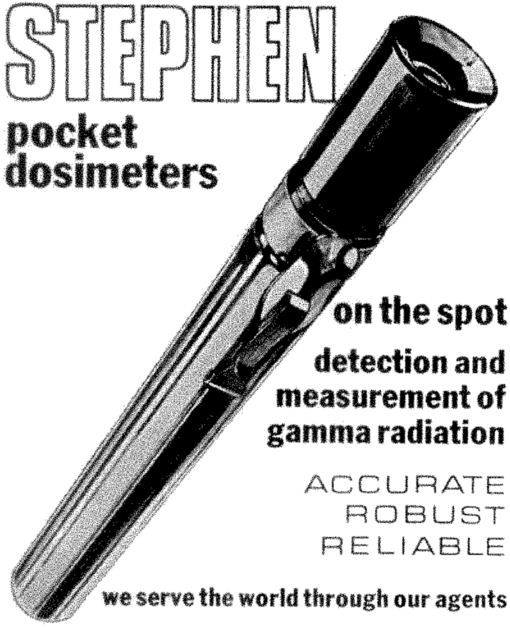


digiecho 2000

- rapid measurement rate
- selectable number of readings
- microprocessor controlled
- automatic printed record

DIAGNOSTIC SONAR LTD

1 Grange Road, Houstoun Industrial Estate, Livingston EH54 5DE, Scotland, U.K.
Tel. Livingston (STD Code 0589) 35165/6. Cable address: Sonar Livingston. Telex: 72591 DSONAR


STEPHEN
pocket dosimeters
on the spot detection and measurement of gamma radiation
ACCURATE
ROBUST
RELIABLE
we serve the world through our agents

R·A·Stephen
AND COMPANY LIMITED
Miles Road Mitcham CR4 3YP Tel 01-648 1668/9

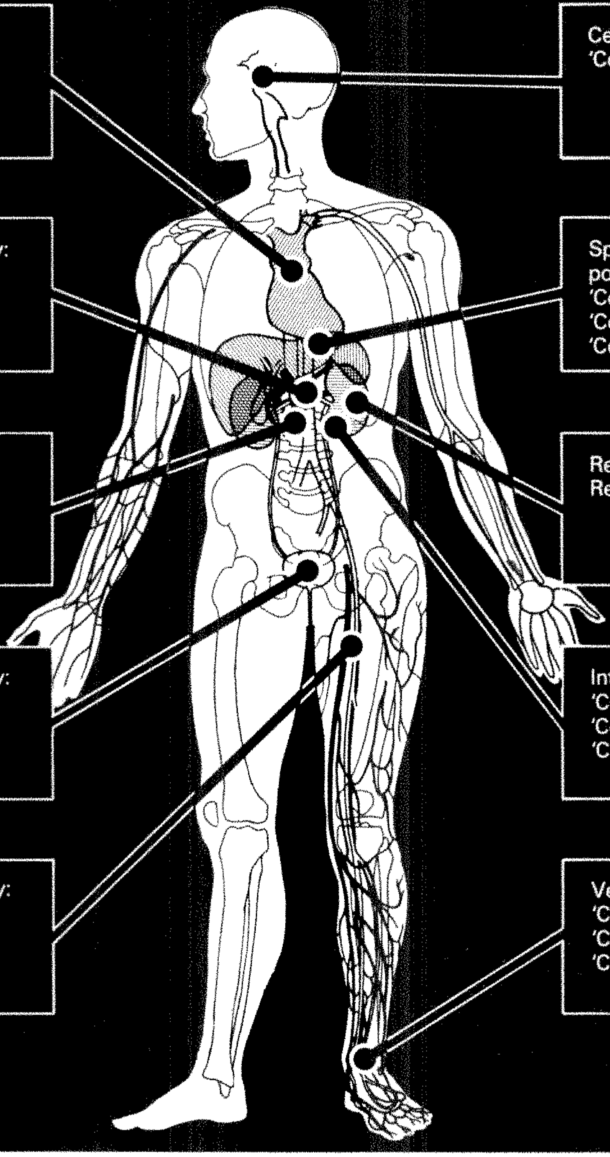
WANTED

DIAGNOSTIC RADIOLOGIST

required for group in large western Canadian city. Training in ultrasound, mammography and Nuclear Medicine an asset. Private clinic practice and hospital affiliation. Please reply to Box No. 7, British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Required: Second-hand Kodak Continuous Film Dryers in full working order and any available spare parts.

Contact by Air Mail: Dr. Waguih Tawfik, Assiut University Hospital, Assiut, Egypt.



The 'CONRAY' range of contrast media puts your patient fully in the picture

Angio-cardiography:
Cardio – 'Conray':
'Conray 420':
'Conray 280'

Cerebral angiography:
'Conray 280'

Abdominal-aortography:
'Conray 280':
'Conray 420':
'Conray 325':
Cardio – 'Conray'

Splenography and
portal venography:
'Conray 280':
'Conray 420':
'Conray 325'

Gastroenterography:
Gastro – 'Conray'

Retrograde pyelography:
Retro – 'Conray'

Retrograde cystography:
'Conray 280':
'Conray 420'
(suitably diluted)

Intravenous urography:
'Conray 325':
'Conray 420':
'Conray 280'

Peripheral arteriography:
'Conray 280'

Venography:
'Conray 280':
'Conray 420':
'Conray 325'

Conray Contrast Media

There is a wide variety of formulations and almost certainly one to meet your specific requirements however exacting they may be.

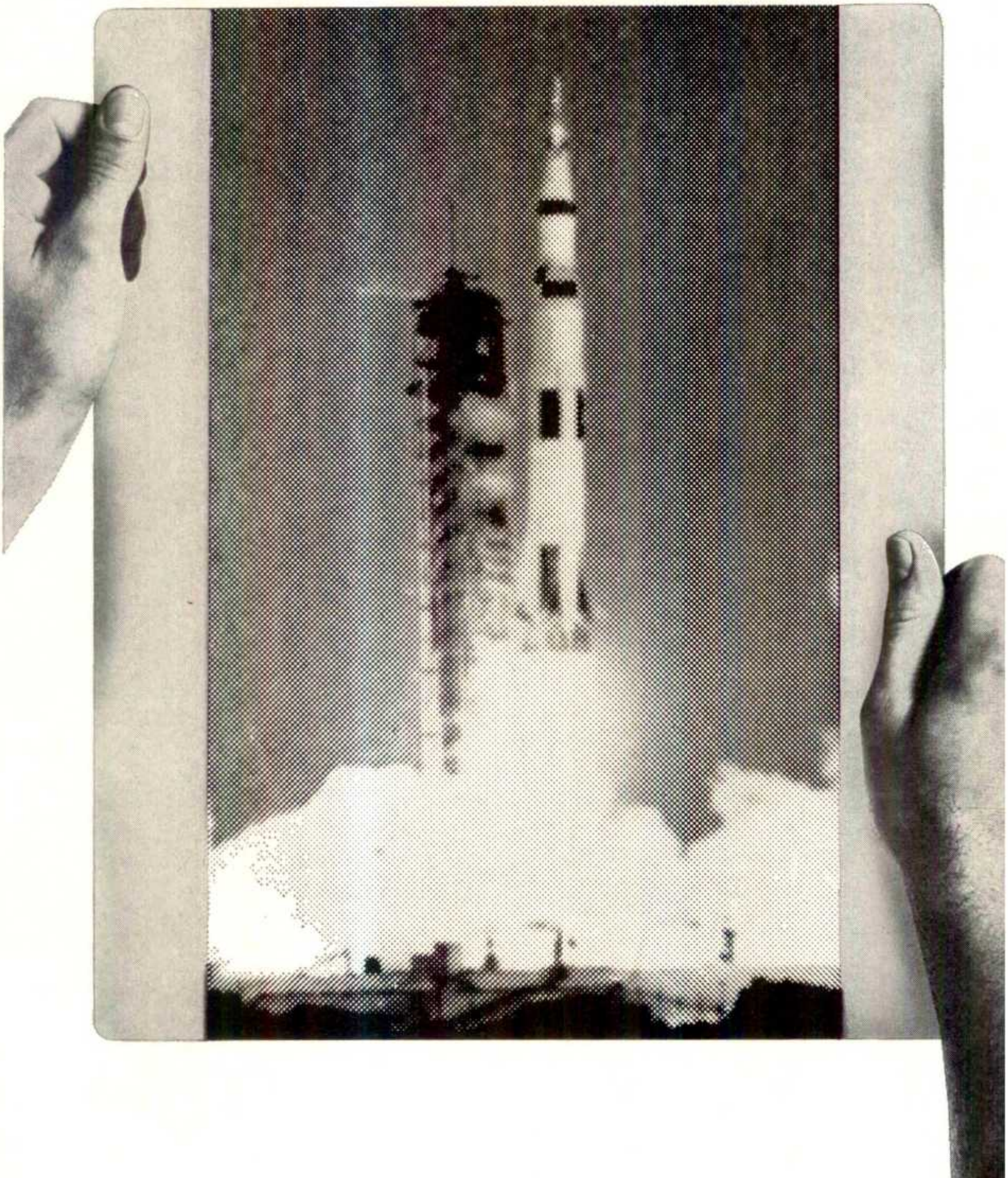
'Conray'* contrast media are formulations of meglumine iothalamate, sodium iothalamate or combinations of the two.

Full information supplied on request to
May & Baker Ltd Dagenham Essex RM10 7XS
*trade mark of Mallinckrodt Inc.

M&B May&Baker

A member of the Rhône-Poulenc Group of Companies

MA 6535



ILFORD shows up everywhere.

The performance you expect – and get from ILFORD X-ray materials shows up in many other, sometimes unexpected places.

For if there's an image to be recorded, ILFORD will seldom be far away.

Our Microfilm products show up in the computer world recording output and in the fields of finance and industry with image retrieval systems. And again in the security recording of the massive weekly tide of football pool coupons.

We show up again in newspapers and magazines where ILFORD films and papers provide the illustrations which are often converted into print by ILFORD Graphic Arts materials.

Our Photographic products can show up everywhere from banks (Surveillance film for high security areas) to outer space (Nuclear emulsions as used in every U.S. space shot so far).

In Colour Printing too – amateur or professional – Cibachrome shows up wherever standards really count. You may not see the name, but you will see the results – everywhere.

It is this very involvement in so many fields that supports the broad fundamental research and keeps the ILFORD products you use efficient and up-to-date.

One last thing from ILFORD that always 'shows up': the after sales and technical service.

ILFORD X-RAY

ILFORD Limited, Basildon, Essex.

There's more to ILFORD than meets the eye

AUCKLAND HOSPITAL BOARD

Applications are invited from suitably qualified Medical Practitioners for the position of:

Whole-time specialist Radiologist

Auckland Hospital Board's Hospitals

Positions are available in well equipped hospitals for Radiologists with experience in general radiology and/or the radiological sub-specialities. The Board has an active training programme with twenty-two Registrars who rotate through the hospitals in training for the membership examinations of the Royal Australasian College of Radiologists and the Boards. The Board's training programme is fully accredited by the College.

Salaries will be in accordance with Hospital Services Determination No. M.-9 (Medical Officers) determined by the appointees qualifications and experience within the following scale plus the 3·5% interim Special Allowance calculated on base salary and the June, 1976 Cost of Living Allowance:

Specialist: NZ$17,060–NZ$22,161 with provision for progression beyond NZ$22,161 in recognition of special professional excellence or special responsibility.

Conditions of Appointment and Application Forms are available from:

The Chief Executive, Auckland Hospital Board, P.O. Box 5546, Auckland 1, New Zealand
with whom applications close at noon on Friday, 27th October, 1978.

Northland Hospital Board

RADIOLOGIST

Northland Base Hospital
Whangarei, New Zealand

Applications are invited from practitioners holding suitable post-graduate qualifications in diagnostic radiology for the above position. The Board would consider appointment on a whole-time or part-time basis and opportunities for private radiology exist in the area.

The successful applicant would have a full opportunity to participate in the re-organization and planning of the Radiological Services and a Senior Specialist with suitable experience would be eligible to take over as Head of the Department.

This is a new appointment to facilitate an upgrading in the Board's Radiological Services bringing the number of specialists in the Department to three. Successful applicant would be expected to take part in the teaching and post-graduate work of the hospital.

The Northland Base Hospital has 370 inpatient beds and provides a service in the main specialties for Northland where there are a number of subsidiary peripheral hospitals with a further 300 beds.

Specialist Automatic Scale $17060/$22161 with access to additional steps. Transport expenses to New Zealand available. For further information, Conditions of Appointment and application apply to the undersigned with whom applications close on 29 September 1978:

The Personnel Officer, Northland Hospital Board, P.O. Box 742, Whangarei, NEW ZEALAND.

AXISCAN 5

The new portable real~time ultrasound scanner from Kontron Roche

• Built to a unique design, offering all the facilities you require for obstetric and general abdominal scanning • Truly portable design makes it very easy to use in ante-natal clinics and other departments within hospitals • Simple operation facilitates routine obstetric investigations with the minimum of fuss • Fetal maturity estimations can be established quickly using the integral electronic calipers which automatically reproduce an on-screen digital display. • Results are permanently recorded with the built-in camera. • The excellent grey-scale display shows moving structures up to 25 cm deep. • All our customers are backed by a national 24 hour Kontron Roche service.

KONTRON **ROCHE**

serving hospitals throughout the world

For further information, please complete the coupon below and post to Dr. Hargreaves, Kontron Instruments Ltd., P.O. Box 188, Watford WD2 4YX or telephone Watford (0923) 47666

Please contact me to arrange a demonstration of/send me further information about/ the Axiscan 5.

NAME. . . . .

POSITION . . . .

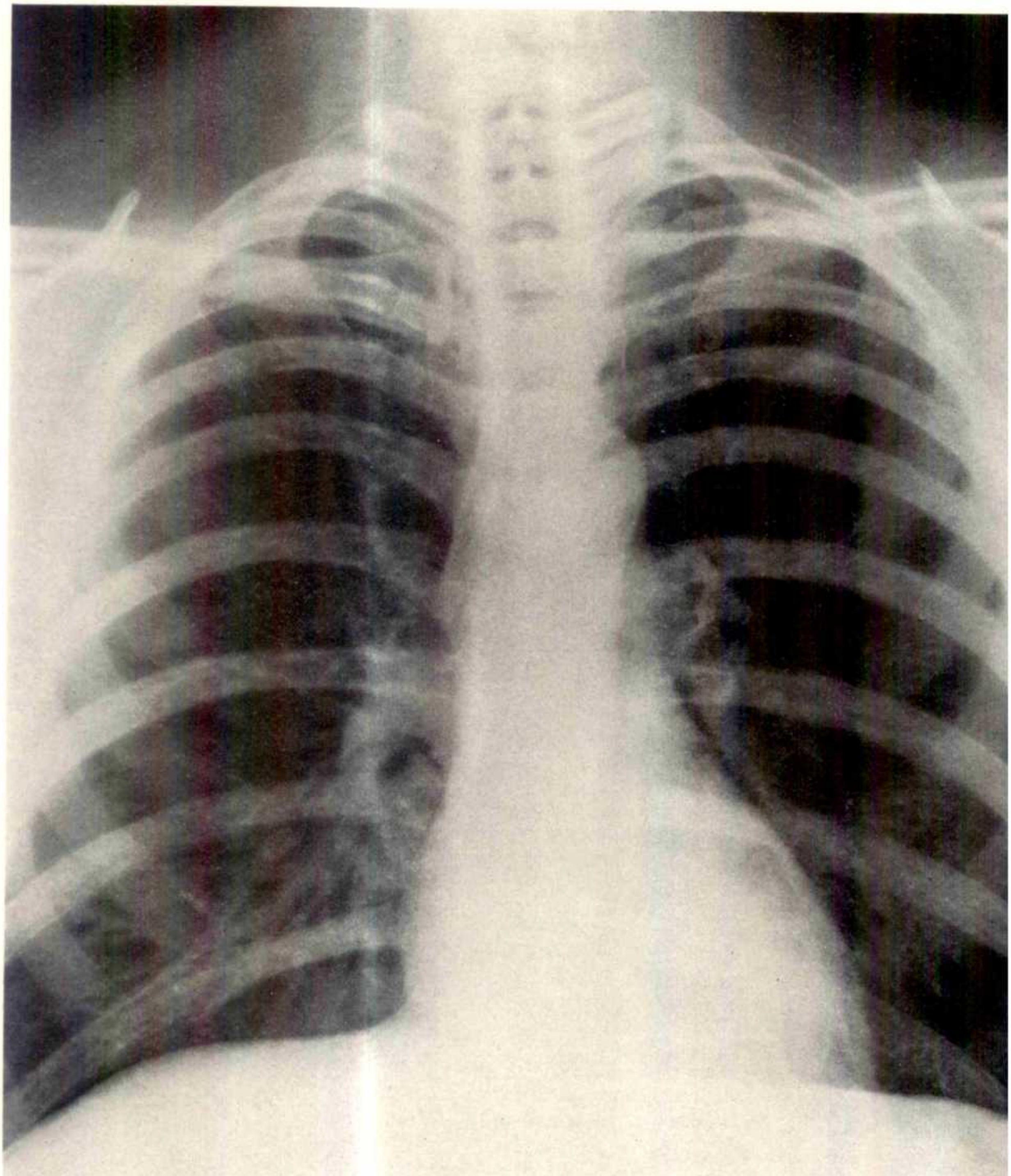
ADDRESS. . . . .

. . . .

. . . .

TELEPHONE. . . . .

Your Kodak



rep wants to get something off his chest

We've been bringing him up to date on the latest developments, and he's got plenty to tell you.

He wants to show you the dramatic exposure reduction and radiographic flexibility that can be achieved with KODAK 'Lanex' screen film combinations. He'll do the demonstration in your department.

He's also got plenty to say about departmental design, ultrasonics, nuclear medicine, instrumentation recording, photography and dental radiography.

He's also prepared to loan you a range of KODAK 'X-Omatic' Cassettes fitted with KODAK 'Lanex' Regular Screens, enabling you to conduct practical tests in your own department.

Ask him about products for mammography-he'll introduce you to the new KODAK 'Min-R' Cassette, designed for use with the KODAK 'Min-R' Screen and KODAK 'Min-R' Film.

When ever you need information, talk to your Kodak Technical Sales Representative. You'll find him professional through and through.

Kodak. We care about your image Kodak

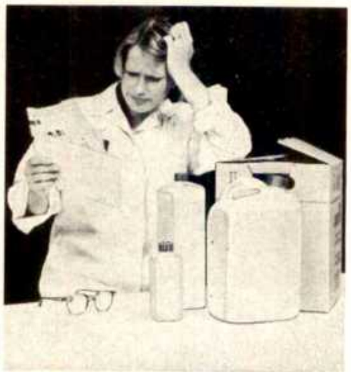
Kodak, Lanex, X-Omatic and Min-R are trade marks.

Before the new C
x-ray chemical mixe
was far from

The old way.

Step 1
Of course you need the right chemicals to begin …

Step 2
next, you must figure out what to do with them (sometimes a bit difficult) …



Step 3
then, get the right amount of water (hopefully from not too far away) …

Step 4
now, pour it in (being careful to keep your shoes dry) …

Step 5
then, add the chemicals (sorry, sometimes chemicals don't smell very good) …

Step 6
finally, mix it all up (we'll bet you're glad you've reached this point in the process. Don't you wish you wouldn't have to do it again next week?).

---

* Du Ponts trademark

RONEX*automatic r, mixing chemicals automatic.

The CRONEX*way.

Step 1
Put in the chemicals.
Close the cover and relax.

Conventional x-ray chemical mixing is complicated, sometimes inexact, and always unpleasant.

Our new CRONEX* automatic chemical mixer puts an end to all that.

This remarkably attractive unit offers fast, uniform mixing by simply installing a boxed container of concentrate. And letting the machine do the rest.

For x-ray technicians it means less work, cleaner working conditions, and no more allergies. Plus fewer mixing errors and better image quality.

The CRONEX* mixer automatically mixes 38 liters each of developer and fixer. Accurately, consistantly and without splash or spill. And if reserve containers of concentrate are installed when solution tank is full, the mixer will automatically make up new developer and fixer when it's needed. That gives it a total capacity of 76 liters.

If you would like to find out more about making your chemical mixing operation automatic, just send the coupon below to:

DU PONT (U.K.) LIMITED, Photo Products Department, Hawkesden Road, St. Neots, Huntingdon, Cambridgeshire PE 19 1QS,
Telephone (04 80) 7 53 41/(01) 2 35 52 86-88
Telex 32159.

DU PONT

☐ **Please send me more information on your new CRONEX*automatic x-ray chemical mixer.**

☐ **Please have a Technical Representative contact me.**

Name: ______________________

Position: ______________________

Company: ______________________

Address: ______________________

The CRONEX*mixer. Close the cover and relax.

The Consultant's diagnosis resulted in an excellent prognosis.

"This will be a great aid to the work of the Department" he said of the Barr & Stroud Rapid Cassette Changer. Its major feature is that it enables 5 serial angiographs to be taken in 5 seconds.

For full details use the journal reply system or call us, Barr & Stroud Limited (Dept. BJR/4), Melrose House, 4–6 Savile Row, London W1X 1AF.
Telephone: 01–437 9652. Telex: 261877

Rapid Cassette Changer SQ13

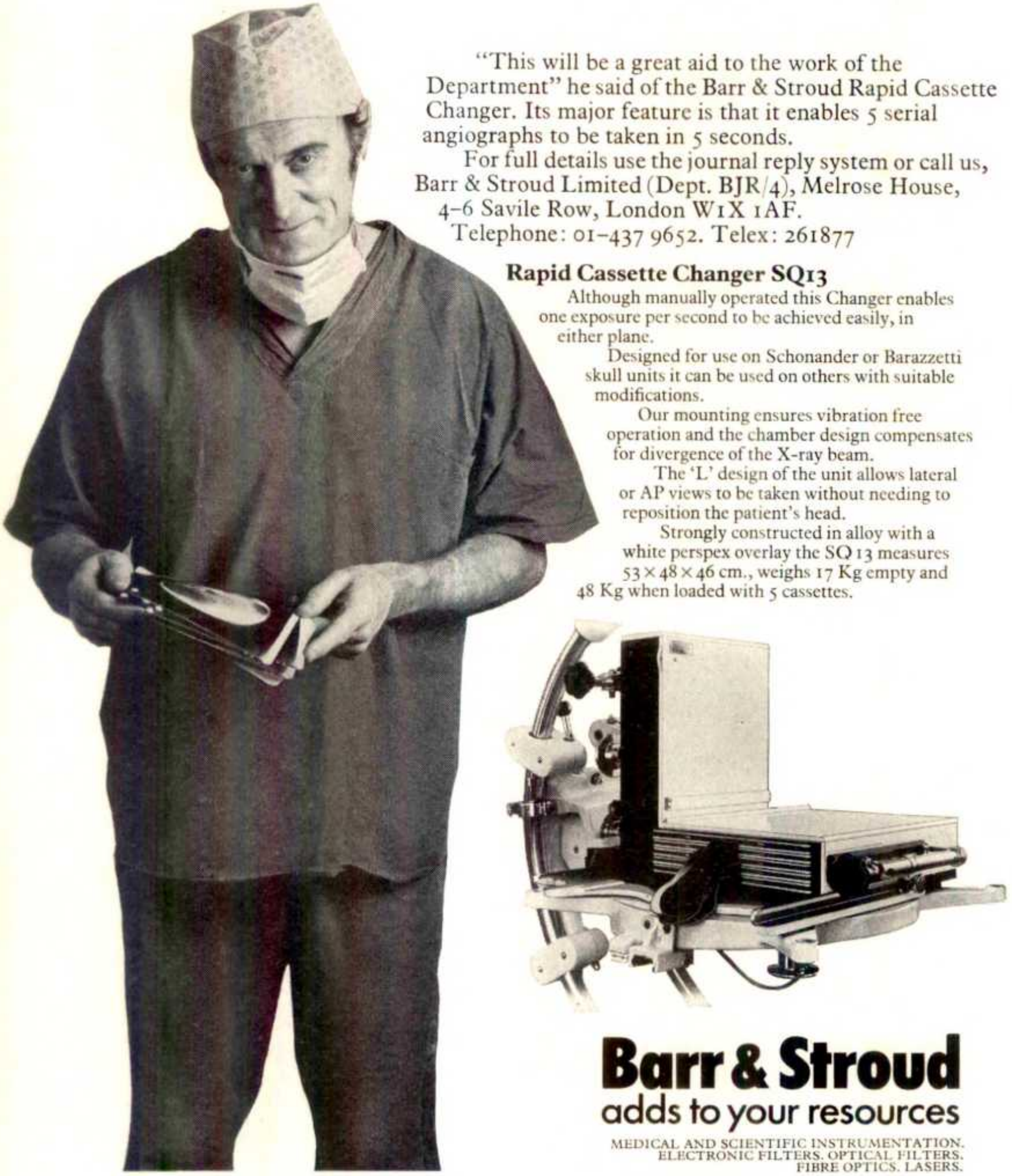
Although manually operated this Changer enables one exposure per second to be achieved easily, in either plane.

Designed for use on Schonander or Barazzetti skull units it can be used on others with suitable modifications.

Our mounting ensures vibration free operation and the chamber design compensates for divergence of the X-ray beam.

The 'L' design of the unit allows lateral or AP views to be taken without needing to reposition the patient's head.

Strongly constructed in alloy with a white perspex overlay the SQ 13 measures 53×48×46 cm., weighs 17 Kg empty and 48 Kg when loaded with 5 cassettes.



Barr & Stroud
adds to your resources

MEDICAL AND SCIENTIFIC INSTRUMENTATION.
ELECTRONIC FILTERS. OPTICAL FILTERS.
FIBRE OPTICS. LASERS.

Dyanne has designs on growing old gracefully.

Dyanne is a clinical data processor for recording manipulating and interpreting static and dynamic studies produced by gamma cameras.

Simplicity of operation is the keynote for everyday use. Data is presented in a clean easy-to-read form and the user may 'access' the raw data whenever required.

Dyanne may be as interactive or as automatic as needs dictate, thus providing an unparalleled level of interaction between the user, computer and gamma camera.

Dyanne has been designed to meet the needs of an expanding technological discipline. Our software will allow you to initiate your own routines and incorporate new procedures through the use of simple protocols.

You can up-date with ease, and this means that you can extend Dyannes' processing capabilities way beyond the limits of less flexible systems.

We're convinced that as soon as you use this powerful data processor it will mark the beginning of a long and industrious relationship. With this in mind we've made sure that in the exciting world of nuclear medicine Dyannes data processing capabilities won't suddenly let you down with an obsolescent bump.

LINK SYSTEMS

Halifax Road, High Wycombe,
Bucks. HP12 3SE, England.
Tel: 0494 24145 Telex: 837542

Worldwide sales and service

RADIOLOGY STUDY GUIDE

for passing the F.R.C.R. II

by KEITH SIMPKINS

Printed by
the University of
Leeds Printing Service
215 pages, 17 illustrations
more than 400 key refererences

A unique consumer's handbook for success in Diagnostic Radiology examinations, providing a route map between D.M.R.D. and F.R.C.R. II. Packed with sound advice and useful information, and laced with controversy and humour.

Price £5·50 (U.K.)
or £6·50 (overseas) inc. p+p.

Obtainable from

Dr. K. C. Simpkins, Department of Diagnostic Radiology,
The General Infirmary at Leeds,
Leeds LS1 3EX.

British Journal of Radiology

TEACHING BOOKLETS

No. 1
The Physical Aspects of Radioisotopic Organ Imaging, by K. G. Leach (1976) £1·50

No. 2
Introduction to the Principles of Diagnostic Ultrasound, by H. B. Meire and P. Armstrong (1976) £1·40

No. 3
Fundamental Aspects of Medical Thermography, by W. M. Park and B. L. Reece (1976) £3·40

Available from the Publications Office,
British Institute of Radiology,
32 Welbeck Street, London W1M 7PG

ROCHDALE AREA HEALTH AUTHORITY

ROCHDALE INFIRMARY

LOCUM CONSULTANT RADIOLOGIST

Required immediately, to the Rochdale Group of Hospitals. This post will be offered initially for a period of three months, during which time the substansive post will be advertised.

Candidates should possess wide experience in radiology and an appropriate higher qualification.

For further information please contact Dr. R. Bullough, Area Specialist, Telegraph House, Baillie Street, Rochdale. Telephone Rochdale (0706) 47391.

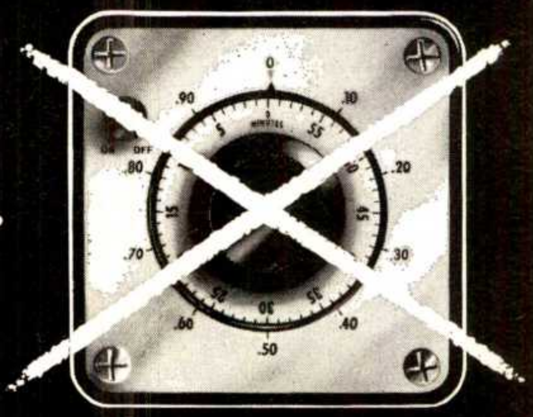
Applications in writing to the Area Personnel Officer, Birch Hill Hospital, Rochdale, Lancashire OL12 9QB.

DIAGNOSTIC RADIOLOGIST

to work in private radiology office. Full or part time. Locum acceptable. Interested applicant must have taken his undergraduate training in the British Commonwealth and must be a fully qualified radiologist. Salary negotiable.

Please address replies to:
Dr. I. D. Hendin, Suite 210, 8409-122 Street, Edmonton, Alberta, Canada. T6G 1K6 or telephone collect (403) 433-2588 or (403) 436-3133.

The time...



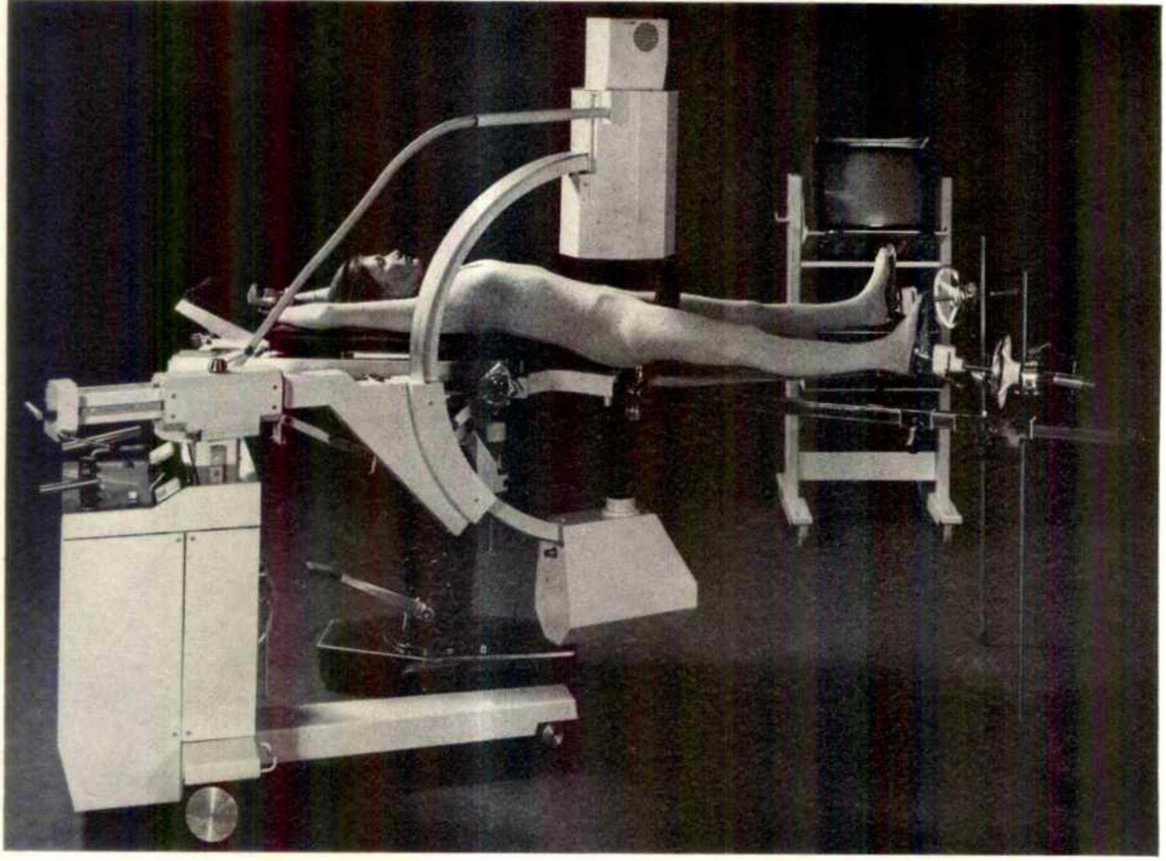
has come!

. . . to meet the requirements called for in the recommendations of the Radiotherapy Apparatus Safety Measures Panel Document R.A.S.M.P.75. Section 3, paragraph 3.11. THE TEM DIGITAL CONTROL TIMER for therapy units has been specifically designed with this in mind. To enable the Timer to be used with existing equipment, the setting and display section will fit into approximately the same space as a conventional Timer. Alternatively, the unit complete with power pack can be supplied as a separate free standing unit.

TEM Instruments Limited

Gatwick Road, Crawley, Sussex, RH10 2RG, England Tel 0293 31244
Telex 87397, Grams TESTMENT CRAWLEY

A rapid and precise surgical X-ray system with high-resolution TV



The streamline design for the CGR Optascop increases the range of applications in surgical radiology. Easier manipulation and greater mobility by steering castors allow precise positioning from the simplified control panel.

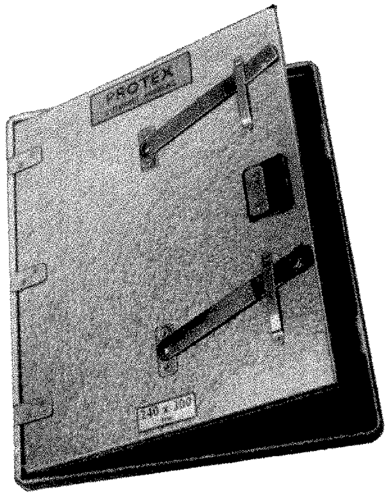
A complete mobile high-definition intensifier unit equipped with a TV camera and separate trolley-mounted monitor.

The dual focus x-ray tube with remote controlled collimator provides for radiography and fluoroscopy up to 100kV. The x-ray tube – intensifier TV movements are motor driven.

Optional extras are dose reduction pulsed fluoroscopy, and taped memory facility.

OPTASCOP
from
CGR

Full details and specification from
CGR MEDICAL LIMITED
Astronaut House, Feltham, Middx. Tel: 01-890 8166



BEAUTY IS BUT SKIN DEEP

Our "Protex" cassette may not be the most beautiful on the market, nor the lightest, nor the shiniest – but then it was never intended to be.

So much criticism was levelled at cassette design during the late sixties that we introduced in 1970 a hand-made unit to eliminate the various weaknesses in certain makes at that time.

Within a year or two we were obliged to discontinue advertising the new cassette as demand had outstripped supply.

Although still hand-made, output has improved considerably and we can again draw your attention to the advantages of the tray-shaped aluminium front rivetted into a folded steel frame and the simple latch fastenings lying flat to avoid damage.

CUTHBERT ANDREWS
EVERYTHING X-RAY LTD.
5 HIGH STREET, BUSHEY VILLAGE, WATFORD WD2 IBE
Overseas telegrams: EXRAYZE WATFORD
Telephone: 01-950 2525

APPEAL

A permanent home for British radiology

The Appeal Committee

Sir Jan Lewando, CBE (Chairman)
Dr. Julian Bloom
The Lord Hunt of Fawley, CBE
Mr. Kevin Hughes
Sir Peter Kerley, KCVO, CBE
Professor L. F. Lamerton
Sir Thomas Lodge
Dr. J. F. Loutit, CBE, FRS
Professor W. V. Mayneord, CBE, FRS
Professor J. H. Middlemiss, CMG
The Lord Penney, OM, KBE, FRS
Sir Edward E. Pochin
Sir John Read
Dr. S. Cochrane Shanks, CBE
Professor Sir David Smithers
Professor R. E. Steiner
Dr. Herman D. Suit
Professor Sir Brian Windeyer
The Lord Zuckerman, OM, KCB, FRS
Professor G. H. du Boulay, Appeal Co-Ordinator
The President of the Institute and Appeal Executive Committee members

Funds are needed to secure this new permanent home for The British Institute of Radiology at 36 Portland Place, London W1, next door to the Royal College of Radiologists

Donations and ideas to:
Appeal Co-Ordinator, 32 Welbeck Street, London W1M 7PG (01-935 6237)

1978, *British Journal of Radiology*, *51*, 755
VOLUME 51 NUMBER 610

OCTOBER 1978

The British Journal of Radiology

Editorial

A new home for The British Institute of Radiology

With profound gratitude we are able to announce that a charitable trust which wishes to remain anonymous has purchased No. 36 Portland Place and undertaken its renovation. The British Institute of Radiology will be able to move in when the work is complete. All our efforts must now be bent towards repaying the Trustees, who have shown such extraordinary initiative and generosity and, quite independently of our project, had imaginatively seen the need and worth of Radiology.

BJR readers may be especially interested to reflect that the successful publishing activities of the BIR have increased considerably in recent years. Our new house will provide more space for further growth.

It was to fulfil the declared intentions of The British Institute of Radiology and The Royal College of Radiologists (1973 & 1976) for closer collaboration and co-operative strength that the BIR set out rather more than a year ago to move its headquarters next door to the Royal College's new house. Although there is neither the possibility nor the wish to amalgamate, for such a course would be most destructive to the brotherhood of science and medicine in a learned society, there is every reason to seek proximity so close that economy, mutual understanding and a stronger influence over the future of imaging and therapy can go hand in hand.

The year that has gone by has been a remarkable experience for the officers of the BIR who have had to look for financial support while, at the same time, conducting very difficult negotiations, the success of which depended upon money being available, while rival bids were offered for the house by others.

Two groups of people, in addition to those who manage the charitable trust, have brought us to our present position. First, we must again thank the BIR members who responded so whole-heartedly, thus showing the officers that they had to be totally committed. Secondly, we should be grateful to the BIR's professional advisers who have seen the Institute through a number of extraordinarily difficult decisions.

Much has now to be done to make sure that the BIR's new home is suitable but no burden upon the members.

In addition to what the charitable trust has undertaken, the BIR's appeal has so far raised just under £100,000 in gifts and promises. The appeal target is half a million pounds. Now the Appeal Committee is going to start in earnest, enlisting the help of other trusts, foundations and the leaders of those quite substantial parts of industry and commerce to whom radiology is genuinely important. Not least, the BJR readers by their personal influence as well as their contributions can ensure that in this new home the BIR, with its sister society The Royal College of Radiologists, can care better for the interests of radiology at home and in the world at large.

D. K. Bewley,
F. Starer.

1978, *British Journal of Radiology*, *51*, 756–770

Review article

The current role of cancer chemotherapy

By E. S. Newlands, M.R.C.P., Ph.D.

Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF

(*Received February, 1978 and in revised form March, 1978*)

Abstract

Cancer chemotherapy has developed rapidly over the last twenty years. The majority of patients with cancer die from metastatic disease, so the major therapeutic advance now must be better systemic therapy. From its early beginning in the 1940's with oestrogen therapy for prostatic cancer, nitrogen mustards in the lymphomas, and folic acid antagonists in childhood leukaemia, there are now between thirty and forty active anti-cancer agents in clinical use. The main clinical pharmacological points of the major agents are briefly reviewed, together with their main dose-limiting toxic effects and their activity as single agents.

Clinical chemotherapy has developed by the introduction of newer agents from the drug screening programmes and a better understanding of the scheduling to avoid serious toxicity. Although drug-resistance is still a major problem, by combining different active agents there has been a dramatic improvement in survival of patients with selected tumours. More recently, treatment of patients early, before they have gross clinical recurrence, has already shown some benefit in pre-menopausal patients with carcinoma of the breast and in patients with osteosarcoma. The limitations of clinical measurements in monitoring therapy are clear, and a major improvement could well be realised if therapy could be monitored on the basis of quantitative tumour markers.

The clinical impact of cancer chemotherapy has already been dramatic in drug-sensitive tumours, but these only contribute a small proportion of the total. Some of the common tumours fall into the group that are relatively drug sensitive where the lives of patients can be prolonged, but there is still a significant fraction of tumours which are insensitive to existing drugs and which will probably require the development of newer agents before chemotherapy can make any impact on the survival of patients with these tumours.

The management of an increasing range of tumours has changed rapidly over the last twenty years with the introduction of cancer chemotherapy. In those tumours in which there is a biological tendency for the tumour to remain localized until clinically detectable, local treatment with surgery or radiotherapy (or both) results in a gratifying proportion of "cures" (patients eventually dying of natural causes other than cancer). However, the majority of patients who continue to die from cancer die not from the failure of local treatment but from metastatic disease. This has led to the concept of local treatment for local disease, and systemic treatment for systemic disease. So far cancer chemotherapy is the most effective systemic therapy. Following directly from this has been the development of the multi-modality approach to aggressive tumours in an attempt to get the maximum therapeutic benefit from both local and systemic treatments. As will be discussed, the role of cancer chemotherapy varies widely with the type of tumour being treated, from being the principal form of therapy as in the leukaemias to an unproven role as in metastatic hypernephromas.

While the concept of specific drugs active against cancer goes back to Paul Erhlich, modern cancer chemotherapy started in the 1940's with the observation that oestrogens could induce remissions in some cases of prostatic cancer (Huggins and Hodges, 1941). This was followed by the use of nitrogen mustard to induce remissions in malignant lymphomas (Gilman and Phillips, 1946) and the introduction of folic acid antagonists in childhood leukaemia (Farber *et al.*, 1948). From the original two or three drugs twenty years ago, there are now

TABLE I

Classification of anti-cancer drugs

Class	Examples
Antimetabolites	Methotrexate Fluorouracil Cytosine arabinoside
Alkylating Agents	Cyclophosphamide Melphalan Chlorambucil Nitrogen mustard
Natural Products	
a) Mitotic Inhibitors	Vincristine and vinblastine Podophyllotoxin
b) Antibiotics	Actinomycin D Bleomycin Adriamycin and daunorubicin
c) Enzymes	L-Asparaginase
Random Synthetics	Nitrosoureas, BCNU, CCNU Hydroxyurea Dacarbazine (DTIC) Procarbazine Platinum complexes
Hormones	Cortisone Stilboestrol Progesterone Testosterone

Copies of this article may be obtained from The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG at a cost of 95p; remittance with order please.

between thirty and forty active anti-cancer agents in clinical use. At present cancer chemotherapy can result in normal life expectancy in some patients with ten different types of metastatic cancer (Table VII) and can improve the survival of a proportion of patients with a range of other tumours (Table XII) (De Vita *et al.*, 1975). The rate of change is seen by the fact that in the two years since the review by DeVita *et al.*, in 1975, several of the tumours they classified as drug-intensive would now be included in the responding group of tumours.

CLASSIFICATION AND CLINICAL PHARMACOLOGY

The present classification of anti-cancer agents reflects their disparate origins and, in some cases, the limited knowledge of their mechanism of action. Only a few of the drugs have been developed by biochemical reasoning (*e.g.* 6-mercaptopurine and 5-fluorouracil), while the majority have been picked up by chance observation or by the drug screening programmes (the largest being that run by the National Cancer Institute in the United States). Table I presents one classification of the main types of drugs in clinical use. One of the problems with anti-cancer drugs is that they are toxic to normal cells as well as to tumour cells. They have a low degree of selectivity. Their main cytotoxic effect is on dividing cells and so the most rapidly proliferating cells are preferentially damaged. In the majority of human tumours the rate of cell division is in fact slower than that of the normal bone marrow, gut epithelium and the mucosa of the mouth. This explains the most common pattern of dose-limiting toxicity with these agents (Table II). Given the fact that some normal tissues are proliferating faster than most cancers, it is surprising that in certain tumours such a selective cytotoxic action is seen. The basis of this selectivity is largely unknown but it is likely that a major part of it is pharmacological. Extensive investigation of the biochemistry of tumour cells has so far uncovered only quantitative differences between cancer cells and normal cells. At present there is no truly "cancer specific" biochemical pathway to exploit.

The kinetic pattern of growth of tumours may also be important in the selective cytotoxic action seen in some cancers. In fact there is a paradox in human cancers: if human tumours grew as fast as the animal screening models (such as L1210 leukaemia), response and cure rates might be better than they are. Bruce *et al.*, (1966) proposed a classification of cytotoxic agents on the basis of the relative effectiveness of drugs to reduce the clonogenic cells (stem cells capable of reconstituting a population) in normal bone marrow and lymphoma cells in mice. They defined three classes of anti-tumour compound:

Class 1 Non-cell-cycle specific agents which kill cells whether they are dividing or not, *e.g.* irradiation and nitrogen mustard.

Class 2 Cell-cycle phase-specific agents which kill cells in only one phase of the cell cycle such as "S" phase (the period of DNA synthesis) or mitosis. Examples: vincristine, methotrexate and cytosine arabinoside.

Class 3 Cell-cycle specific agents which kill cells at all phases of the cell cycle *e.g.* cyclophosphamide, 5-fluorouracil and actinomycin D.

With the rapidly proliferating lymphoma cells which Bruce and his co-workers studied, the selective action of Class 2 and 3 agents against the

TABLE II

DOSE LIMITING TOXICITY OF CYTOTOXIC DRUGS

Bone Marrow	Methotrexate Cytosine arabinoside Mercaptopurine Thioguanine Fluorouracil Cyclophosphamide	Busulphan Chlorambucil Mustine BCNU, CCNU Procarbazine Actinomycin D	Melphalan Adriamycin Daunorubicin Mitomycin C Vinblastine
Mucosal	Actinomycin D Adriamycin Bleomycin	Methotrexate Fluorouracil Daunorubicin	
Cardiac	Adriamycin	Daunorubicin	
Pulmonary	Bleomycin		
Renal	Cis platinum	Methotrexate (High Dose)	
Peripheral Neuropathy	Vincristine		

lymphoma cells depended on the kinetic differences in the cell cycle between the tumour and normal bone marrow. It is difficult to translate this attractive model system directly into clinical practice, since the kinetics of human tumours are so different. With the relatively slow-growing human tumours, one cannot expect to get so selective an action because the proportion of tumour cells in cell cycle at any one moment is low when compared with some of the normal tissues. One physiological feature which has been neglected in the study of tumour cell kinetics in relation to selective drug action is the differential rate of recovery between normal and tumour cells following a cytotoxic drug. This can be seen in choriocarcinoma where the tumour growth pattern is accurately reflected in the production of human chorionic gonadotrophin (hCG). In those tumours which are initially drug sensitive there is a preferential cytotoxic action against the tumour but, if drug resistance develops, the recovery of the tumour following each treatment can become as rapid as the recovery of the normal tissues. If the process of drug resistance becomes more extreme, then one definition of a therapeutic failure is the situation where there is a more rapid recovery of the tumour than the normal tissues.

The toxic side effects of anti-cancer drugs can be limited, and in some cases, such as methotrexate with folinic acid rescue, they can be entirely abrogated by an adequate understanding of the clinical pharmacology of the drugs. The major dose-limiting features of some of the drugs are listed in Table II. There are recent reviews of the pharmacology of anti-cancer drugs by Chabner *et al.*, (1975) and Tattersall (1975). A tabular form of the main single-agent activity against solid tumours of the major drugs has also been presented by Wasserman *et al.*, (1975). A point which is clearly presented in this article is that many drugs have not been adequately assessed in particular tumours, and in some common cancers almost no evaluation of drugs has yet been done. As will be seen in this brief review of the main anti-cancer agents, their range of activity is closely related to the tissue of origin of the tumour; some have a narrow spectrum such as the vinca alkaloids, and some have a relatively broad spectrum such as adriamycin.

From the patient's point of view, the most unpleasant side effect of certain of the anti-cancer drugs is nausea and vomiting. The severity of this varies widely between patients and is still only partially controlled by anti-emetics. Alopecia occurs to a varying degree with a range of the drugs, but is always reversible when chemotherapy stops and commonly the hair re-grows despite continuing therapy. Mucositis can be very unpleasant but, like the myelosuppression, is reversible over a period of five to ten days, reflecting the rapid recovery phase of the normal tissues. With certain exceptions such as the cumulative toxicities with adriamycin, bleomycin and cis-platinum (Table II), the common toxicities of the anti-cancer drugs are usually reversible within two to three weeks. Ovarian function is usually only temporarily suppressed whereas the effect on spermatogenesis is more profound and long-lasting.

Anti-Metabolites

An anti-metabolite is any compound which by virtue of chemical similarity interferes with the utilization of a natural metabolite. In practice, those in use clinically are either analogues of nucleic acid precursors, or of folic acid. Examples of pyrimidine analogues which are anti-metabolites are cytosine arabinoside, 5-fluorouracil, azacytidine and azauridine; examples of purine analogues in use are 6-mercaptopurine and 6-thioguanine. At present the main anti-folate in use is methotrexate. All the nucleic acid anti-metabolites are extensively metabolized both to active and inactive forms. Therefore the sensitivity of a tumour to these compounds depends in part on the pattern of activation and the rate of degradation of each drug.

Methotrexate inhibits the production of reduced folates by competitively binding to the enzyme dihydrofolate reductase. The normal products of the enzyme, tetrahydrofolates, are necessary for both purine and pyrimidine biosynthesis. Methotrexate requires active transport into cells and therefore resistance can occur through inadequate penetration into the tumour cells. Penetration of methotrexate into the cerebrospinal fluid is also poor and adequate therapy of the central nervous system and meningeal disease requires either intrathecal therapy (Bagshawe *et al.*, 1969) or high-dose systemic therapy (Pitman *et al.*, 1975). While there is some entero-hepatic metabolism of methotrexate, the dominant excretion is renal. Methotrexate can be given orally, intramuscularly or intravenously. The toxicity is closely

TABLE III

CYTOTOXIC DRUGS EXCRETED IN URINE

Methotrexate*	Daunorubicin	Dacarbazine
Azauridine*	Actinomycin D	Bleomycin
Cis-platinum*	Mitomycin	Hydroxyurea
Adriamycin		

*Dosage reduction indicated if renal function is abnormal.

related to the dose given and to the renal clearance (Table III). The enzymatic block produced by methotrexate can be by-passed by giving a reduced folate, folinic acid (this can be given orally, intramuscularly or intravenously). This reversal of the action of methotrexate is commonly referred to as folinic acid "rescue" and is usually given between 24 and 36 hours after the methotrexate. Given normal renal function and an adequate dose of folinic acid, up to 20 g of methotrexate per m^2 of body surface can be given without toxicity. Some tumours such as choriocarcinoma and lymphoblastic leukaemia are very sensitive to low-dose methotrexate, while others such as head and neck carcinoma respond better to high-dose methotrexate (Levitt *et al.*, 1973). Over the last few years there has been great interest in using high-dose methotrexate with folinic acid as outlined above, but so far there are few studies which have clearly shown that high-dose is superior to low-dose methotrexate in a particular tumour. The clearance of methotrexate is slowed by its persistence in effusions and ascites and this can result in severe toxicity. Septrin is a drug containing two anti-folates which also enhances methotrexate toxicity when it is given without folinic acid rescue. The main established clinical activity of methotrexate includes: acute lymphoblastic leukaemia, malignant lymphomas, choriocarcinoma, carcinomas of the breast and bronchus, squamous cell carcinoma of the head and neck and osteosarcomas.

5-fluorouracil was synthesized by Heidelberger (Duschinsky *et al.*, 1957) following the observation that hepatoma cells preferentially incorporated uracil precursors into thymidine. Unlike the other anti-metabolites, 5-fluorouracil is active throughout the cell cycle and is not limited to the phase of DNA synthesis (S phase). 5-fluorouracil requires activation to fluorodeoxyuridine monophosphate which inhibits thymidylate synthetase. 5-fluorouracil is usually administered intravenously since absorption from the gastro-intestinal tract is variable. It may also be administered topically or into effusions. 5-fluorouracil is mainly metabolized in the liver. Its penetration into all tissues is good, including the central nervous system and effusions. The optimal schedule of administration is still not clear for most tumours. Its main clinical activity is in carcinoma of the breast, stomach, colon, pancreas, ovary and cervix.

Cytosine arabinoside is a pyrimidine nucleoside analogue which competitively inhibits DNA polymerase after activation to arabinoside cytidine triphosphate (Furth and Cohen 1968). Important aspects of the anti-tumour activity of cytosine arabinoside are the relative activities of the kinase which activates cytosine arabinoside and the deaminase which converts the drug into an inactive form. Cytosine arabinoside can be given intravenously, intramuscularly and subcutaneously. Following an intravenous bolus, the drug is rapidly excreted in the urine and inactivated by the deaminase enzymes in the red blood cells and in the liver. This is important for the scheduling of cytosine arabinoside: continuous infusions are more effective than a single bolus both in animals (Skipper *et al.*, 1967) and in man (Mellett, 1972). The main use of cytosine arabinoside clinically is in acute lymphoblastic and acute myeloblastic leukaemias.

Alkylating agents

These compounds react covalently with many cell constituents. The clinically useful ones are polyfunctional (usually two active groups) and their main activity is probably by inducing intra- and interstrand linking of DNA so that it loses its template activity. The activity of these agents is by the production of a positively-charged carbonium ion or

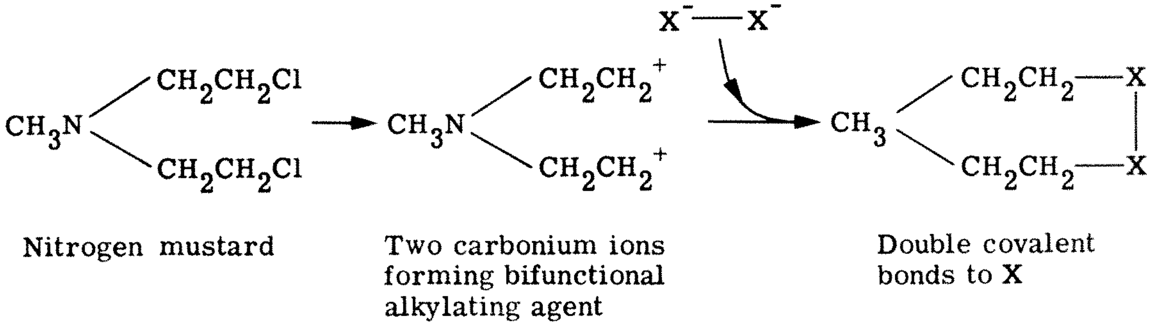


Fig. 1.

Mechanism of action of a bifunctional alkylating agent.

ions (Fig. 1) which reacts avidly with negatively-charged molecules such as nucleic acids. Because these compounds are so reactive with many cell constituents, the exact cause of their cytotoxic activity is still not clear. This has made it difficult to identify the factors underlying the differential sensitivity of tumours to different alkylating agents. Resistance to one alkylating agent does not necessarily imply resistance to all others (Connors, 1975; Schabel, 1975). Alkylating agents react with non-dividing cells but their cytotoxic action becomes manifest once the cells start to divide. One cause of resistance to alkylating agents is the increased rate of DNA repair that can occur in tumour cells. The neoplastic cells can become biochemically more efficient than normal tissues at repairing the damage done by alkylating agents.

Cyclophosphamide is inactive until metabolized by the hepatic microsomes. A range of products is formed and it is probable that the main active compounds are phosphoramide mustard and acrolein (Connors *et al.*, 1974). Variation in the rate of activation of cyclophosphamide and the pattern of active metabolites produced may account for some of the selectivity seen clinically with the drug. Cyclophosphamide can be given intravenously or orally. Nausea and vomiting can be severe in some patients. Particular side effects which can occur with cyclophosphamide are haemorrhagic cystitis and gonadal suppression (the testes are more affected than the ovaries). It is also an immuno-suppressive agent. The main clinical activity of cyclophosphamide includes the malignant lymphomas, lymphoblastic leukaemia, carcinomas of the bronchus, breast, ovary and sarcomas.

Melphalan or phenylalanine mustard has been used widely in selected tumours: multiple myeloma, carcinoma of the breast and ovary, and also in malignant teratomas. It can be given orally or intravenously and has few symptomatic side effects. Oral absorption is incomplete (Tattersall *et al.*, 1978) and may account for some of the variation seen clinically. It is one of the cytotoxic agents with more prolonged myelosuppression (up to six weeks in some cases). Chlorambucil is another alkylating agent with few symptomatic side effects. Its main uses have been in chronic lymphocytic leukaemia, malignant lymphomas, and in carcinomas of the breast and ovary. Nitrogen mustard (mustine) was the first cytotoxic agent used in cancer chemotherapy in 1942. Its proposed mechanism of action is shown in Fig. 1. This is thought to be representative of the cytotoxic action of the other bifunctional alkylating agents. Nitrogen mustard induces moderately severe nausea and vomiting and is a notable sclerosing agent. Its main clinical uses have been in carcinoma of the bronchus, ovary and in the malignant lymphomas.

Since some cells have specific hormone receptors, one of the more recent developments with the alkylating agents is to bind them covalently to hormones. By doing this, it is hoped that a specific delivery of the alkylating agent in a relatively non-toxic form will increase the selectivity of the drug without increasing the toxicity. At present there are two clinically available alkylating agents bound to hormones. These are: estracyt (oestradiol coupled to nitrogen mustard) which has some activity in prostatic carcinoma, and prednimustine (prednisolone coupled to chlorambucil) which has activity in malignant lymphomas.

Natural products

(*a*) *Mitotic inhibitors*

The vinca alkaloids are derived from the periwinkle. Both vincristine and vinblastine bind to the microtubules (Benesch and Malawista, 1969) and cause dissolution of the mitotic spindle apparatus (Sartorelli and Creasey, 1969). Vincristine is unusual in having peripheral neuropathy as a dose-limiting toxicity, while vinblastine is more myelosuppressive. They must be administered intravenously and are mainly excreted in the bile. Dosage reduction is necessary if liver function is severely impaired (Table IV). The main clinical uses of the vinca alkaloids are in leukaemias, lymphomas, carcinoma of the breast, malignant teratomas and sarcomas.

Podophyllotoxin is an extract from the American mandrake; recently two semi-synthetic derivatives (VM-26 and VP16-213) have been studied in selected tumours. The parent compound inhibits cell division by binding to the mitotic spindle, but the semi-synthetic derivatives may have a more direct action on DNA by inducing single strand breaks in it (Horwitz and Loike, 1977). Clinical activity has been found in the leukaemias and lymphomas with VM-26 and in oat cell carcinoma of the bronchus and malignant teratomas with VP16-213 (Rozencweig *et al.*, 1977b).

TABLE IV

Cytotoxic drugs catabolized or excreted by the liver

Vincristine*	Daunorubicin*	6-Mercaptopurine
Vinblastine*	Methotrexate*	5-Fluorouracil
Adriamycin*	Actinomycin D	Procarbazine

*Dosage reduction indicated if liver function is abnormal.

(*b*) *Antibiotics*

Actinomycin D is derived from *streptomyces* and was isolated in 1954. It binds to DNA and inhibits RNA synthesis. One cause of resistance that can be demonstrated experimentally is reduced permeability into the resistant tumour cells. Actinomycin D is a sclerosent and must be administered intravenously. Nausea and vomiting is common and mucositis and myelosuppression are dose limiting. It has a long half-life in tissue and two thirds of an administered dose are retained during the first nine days (Tattersall *et al.*, 1975). Its main clinical activity is in the lymphomas, teratomas, choriocarcinoma, Wilm's tumour, Ewing's sarcoma and other sarcomas.

Bleomycin is a group of polypeptides produced by *streptomyces verticullus* (Umezawa *et al.*, 1966). It reacts with DNA and causes single-strand breaks in it (Suzuki *et al.*, 1968). It tends to be concentrated in squamous cells and this may account for some of its preferential activity in tumours of this cell type. Excretion is mainly renal. It can be given intravenously, intramuscularly or subcutaneously. The optimum schedule of administration has not yet been determined. Unlike most cytotoxic agents, it has little myelosuppressive activity and its dose-limiting toxicity is in the skin, mucosa and lungs. Pulmonary fibrosis occurs with cumulative dose and the total dose given is usually limited to 300 mg because of this complication. Pyrexia, presumably due to hypersensitivity, is relatively common, but anaphylaxis is rare. The main clinical activity is in malignant lymphomas, squamous cell carcinoma of the head and neck and malignant teratomas.

The anthracycline antibiotics, adriamycin and daunorubicin, are derived from the fungus *streptomyces peucetius var. caesius.* The two compounds differ only by the presence of a hydroxyl group in adriamycin, but this has a significant effect on the spectrum of activity and the dose given. The activity of both drugs is due to their affinity for DNA. They intercalate or lie between the strands of DNA causing loss of template function (Di Marco *et al.*, 1969; Pigram *et al.*, 1972). The excretion of both drugs is largely biliary and therefore dosage reduction is necessary with impaired liver function (Table IV). Both drugs are given intravenously and the usual schedule is a single dose repeated at intervals of three weeks. The acute toxicity of both drugs includes nausea and vomiting, alopecia, reversible mucositis, and myelosuppression. Both drugs are concentrated in the myocardium and cause dose-related cardiomyopathy. The current policy is to limit the total dose of both drugs to 550 mg/m^2 (Lefrak *et al.*, 1973). Where they are given with either cyclophosphamide or mediastinal irradiation, the dose is further lowered to 450 mg/m^2. The comparable effective dose (in mg) of adriamycin is lower than that for daunorubicin and therefore more adriamycin can be given before the cardiotoxic dose is reached. The main clinical activity of daunorubicin is in the acute leukaemias. Adriamycin has a wider spectrum and, in addition to the leukaemias, has activity in the malignant lymphomas, carcinomas of the bronchus, breast, ovary and bladder, sarcomas hepatomas and thyroid carcinoma. There is much current research looking for less toxic analogues of these very useful anti-cancer drugs.

Enzymes

L-asparaginase was discovered by the observation that guinea pig serum had anti-tumour activity in some murine tumours (Kidd 1953). Some tumour cells lack the endogenous capacity to synthesize asparagine. In these cases, depletion of serum asparagine by asparaginase can result in tumour cell death. The clinical preparations are derived from *E. Coli* or *Erwinia* and, as a foreign bacterial protein, can induce anaphylaxis. It is not myelosuppressive but can induce vomiting, pyrexia and liver damage. Its clinical use is limited to acute lymphoblastic leukaemia and malignant lymphomas.

Random synthetics

The nitrosoureas have been recognized as effective anti-tumour agents in various animal tumours since 1963 (Johnston *et al.*, 1963). They may act in part as alkylating agents but, as the compounds react rapidly, the specific active metabolites which are cytotoxic have not been identified. Little is known about the pharmacokinetics of these compounds in man, but their lipid solubility means that there is good CNS penetration and some activity has been found in both primary and secondary intra-cranial tumours. Bischloroethyl nitrosourea (BCNU) is given intravenously and chloroethylcyclohexyl nitrosourea (CCNU) is given orally. They cause some nausea and vomiting but their greatest limitation is the prolonged myelosuppression they can induce. Newer compounds with less myelosuppressive activity are currently being studied. The main uses of BCNU and CCNU in man are in the malignant lymphomas, intracerebral tumours, carcinomas of the breast and bronchus, and they have some minor activity in malignant melanoma and carcinoma of the colon.

Hydroxyurea inhibitis pyrimidine biosynthesis by inhibiting the enzyme ribonucleotide reductase. The absorption from the gastrointestinal tract is good and the drug is well tolerated. It is rapidly excreted in the urine and it is possible that greater anti-tumour effect would be gained by giving small doses more frequently than the usual divided doses three or four times a day. At present its established clinical use is limited to resistant chronic myeloid leukaemia. Some occasional responses have been recorded in malignant melanoma, hypernephromas and carcinomas of the stomach and colon.

Decarbazine (DTIC) is a triazene compound which is light sensitive and is rapidly metabolized. It may also act in part as an alkylating agent. It is given intravenously and usually induces moderately severe nausea and vomiting on the first two days of the normal five-day schedule. When given alone it induces little myelosuppression. Its main uses are in malignant lymphomas, malignant melanomas and sarcomas.

Procarbazine is a hydrazine compound which was synthesized as a monoamine oxidase inhibitor. It is metabolized to as yet unidentified active compounds and its mechanism of action is unknown. It is used clinically in malignant lymphomas and carcinoma of the bronchus. It appears to have reasonable penetration into the central nervous system and responses have been recorded in some primary brain tumours.

A new group of anti-tumour compounds which have recently been extensively studied are the platinum complexes. Rosenberg *et al.*, (1965) observed the anti-bacterial activity of these complexes and later the cytotoxic action was recognized. Platinum complexes bind to DNA and can inactivate its template activity at a concentration too low to induce cross-linking of the DNA strands. The only complex that has had extensive clinical trial so far is Cis-dichlorodiammine platinum (II) (Cis-Platinum) (Rozencweig *et al.*, 1977a). This is given intravenously and induces severe nausea and vomiting. Its main dose-limiting toxicities are its nephrotoxicity and its damage to the eighth nerve. It is currently the most effective single agent in malignant teratomas and also has activity in carcinoma of the ovary and in squamous cell carcinoma of the head and neck; there is also promising activity in carcinoma of the bladder and drug-resistant choriocarcinoma.

Hormones

It has long been recognized that certain tissues and tumours deriving from those tissues are hormone dependent. The first demonstration of this was by Beatson in 1896 who noted remissions in several patients with breast cancer following oophorectomy. The next demonstration of hormone dependence was in 1941 when Huggins and Hodges demonstrated remissions in prostatic carcinoma with orchidectomy. Following the observation that removal of endogenous production of hormones could induce remissions in patients with certain disseminated cancers, there has been extensive study of exogenous hormonal therapy in selected tumours.

Adrenocorticosteroids—The lympholytic properties of the corticosteroids has led to their established use in treating acute lymphoblastic leukaemia, malignant lymphomas including Hodgkin's disease and multiple myeloma. When given in high-dose intermittent schedules many of the complications associated with long-term steroid therapy are avoided. Corticosteroids have also been used in a range of non-lymphoid tumours but they do not have a clear-cut role as cytotoxic agents in these other malignancies. Corticosteroids are of course of considerable use in dealing with other specific complications of malignancy such as hypercalcaemia and oedema around intracranial metastases.

Progestogens—There is now a range of synthetic progestogens available. Their main role is in treating endometrial carcinomas (Kelly and Baker 1961). Responses have also been reported in some patients with carcinoma of the breast and ovary. Responses have also been recorded with hypernephromas (Bloom, 1972).

Oestrogens—The main role of oestrogen therapy has been in recurrent breast carcinoma in post-menopausal women and in metastatic prostatic cancer. In advanced breast cancer, hormonal manipulations either by removing endogenous secretion or by giving exogenous hormones or anti-hormones, gives a response rate of around 30%. More recent work studying oestrogen receptors in breast cancer has shown that those tumours which have detectable oestrogen receptors are more likely to respond to hormonal manipulations than those with no detectable oestrogen receptor (McGuire *et al.*, 1975). In several series the response rate to hormonal manipulations in receptor positive patients is between 50 and 60%, while the response rate in oestrogen-receptor negative patients is around 8%. This predictive test allows better selection of patients for this type of therapy.

Oestrogens have been widely used in treating metastatic prostatic carcinoma. While the majority of patients get subjective relief of symptoms and some show objective tumour regression, the impact of oestrogen therapy on survival is not great (Blackard *et al.*, 1970). There has been much dispute about the dose of oestrogen which should be given in prostatic cancer. On current evidence it seems that stilboestrol 1 mg three times a day is sufficient to suppress androgen production satisfactorily (Bayard *et al.*, 1974) without increasing the vascular complications of oestrogen therapy.

Androgens—The main therapeutic use of androgens is in breast cancer. The objective response rate is approximately 25% in patients treated with androgens. Although some virilization occurs even with the more recent synthetic androgens such as fluoxymesterone, androgens have the additional advantage of promoting protein anabolism in wasted patients.

THE DEVELOPMENT OF CLINICAL CHEMOTHERAPY

One of the characteristics of cancer chemotherapy has been the empirical screening of cytotoxic agents and the trial-and-error development of drug schedules. This has often preceded adequate knowledge of the pharmacology of an individual drug. While this is intellectually unsatisfying, it has allowed a more rapid application of cytotoxic drugs than would have been possible otherwise. More detailed toxicological and pharmacological studies are now done on animals before individual drugs reach the clinic, but in the final analysis animal data are no substitute for clinical studies. Although the majority of anti-tumour agents now in use would be picked up by these drug-screening programmes, there are exceptions such as hexamethylmelamine. This compound has minimal activity in the usual rodent screening tumours and has useful activity in carcinomas of the bronchus, ovary and breast and in lymphomas. It is possible that other useful drugs in human cancer have been missed by the older type of drug screening. A recent improvement in the screening programme has been the introduction of human tumours grown in immune-deprived and nude (T-cell deficient) mice. The human tumours growing in these animals seem to retain many of the growth properties that they had in man. This system screens drugs against human tumours *in vivo* and the early results show a correlation between the experimental and clinical spectrum of anti-tumour activity (Mitchley *et al.*, 1975).

When first used in the 1950's and 1960's the drug scheduling of the few agents available was usually a low dose given continuously until toxicity developed. One example which is still useful is the low-dose continuous use of chlorambucil in follicular lymphomas. However it has been recognized that continuous administration of cytotoxic drugs is particularly effective both in immunosuppressing the patient and in severely compromising the bone marrow reserve (presumably by damaging the stem cells each time they go into cell cycle). Over the years there has been a major switch from low-dose continuous scheduling to high-dose intermittent schemes. There is extensive experimental evidence that the anti-tumour effect of most of the drugs increases with dose (Frei 1974). Another advantage of this is that during the intervals between courses of therapy, the normal bone marrow stem cells and gut

TABLE V

COMPARATIVE RESPONSE RATES BETWEEN SINGLE AGENT THERAPY AND COMBINATION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKAEMIA

Drugs	Percent Complete Bone Marrow Remissions
Methotrexate (M)	22
Mercaptopurine (MP)	27
Prednisone (P)	63
Vincristine (V)	57
Daunorubicin (D)	38
P, V	90
P, V, M, MP	94
P, V, D	100

Modified from Devita *et al.* (1975)

TABLE VI

COMPARATIVE RESPONSE RATES BETWEEN SINGLE AGENT THERAPY AND COMBINATION CHEMOTHERAPY IN ADVANCED BREAST CANCER

Drug	Response Rate (%)
Adriamycin (A)	35
Cyclophosphamide (C)	34
Methotrexate (M)	34
Fluorouracil (F)	26
Vincristine (V)	20
Melphalan	23
CMFVP*	47
CMF	70
AV	63
AC	80
FAC	72

*Prednisone = P
Modified from Carter (1976)

TABLE VII

CANCERS IN WHICH A PROPORTION OF PATIENTS ACHIEVE A NORMAL LIFE SPAN WITH CHEMOTHERAPY

Acute lymphoblastic leukaemia	Embryonal rhadomyosarcoma
Hodgkin's disease	Teratomas
Histiocytic lymphoma	Retinoblastoma
Wilm's tumour	Ewing's sarcoma
Burkitt's lymphoma	Choriocarcinoma

TABLE VIII

Comparative complete response rates between single agent therapy and combination chemotherapy in advanced Hodgkin's disease

Drugs	Complete Response Rates (%)
Mustine (M)	20
Vincristine (oncovin, O)	< 10
Procarbazine (P)	< 10
Prednisone (P)	< 5
MOPP	80

Modified from Devita *et al.* (1975)

TABLE IX

Principles of combination chemotherapy

1.	Each drug should be active as a single agent
2.	Each drug should have a different mechanism of action
3.	Each drug should have a different dose-limiting toxicity

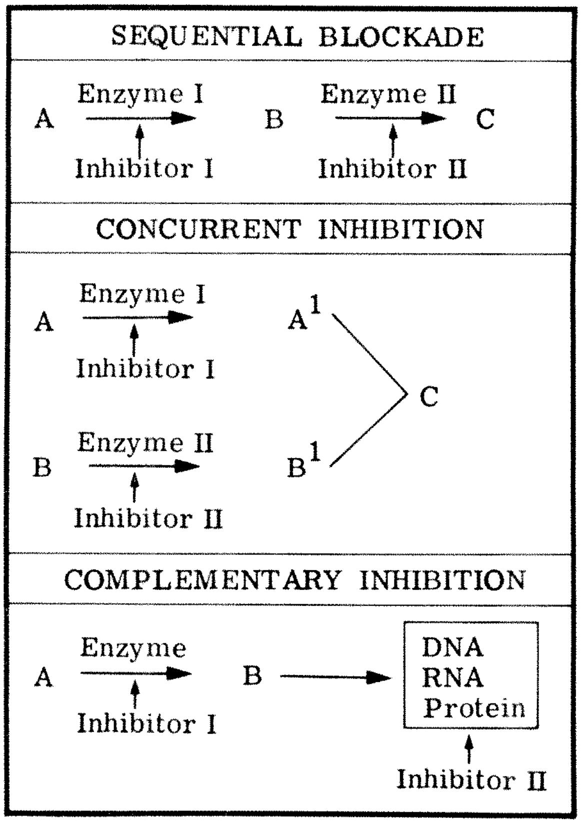


Fig. 2.

Different types of multiple metabolic blockades.

mucosa can recover. The higher tissue concentration obtained with this type of therapy can allow better penetration of the drug into solid-tumour masses.

Combination chemotherapy—Given the fact that, when detected clinically, tumours already contain between 10^8 and 10^{12} tumour cells, it is not surprising that therapy with a single drug at this stage of the disease kills the proportion of cells which are sensitive to it, but leaves the resistant fraction still dividing. This situation is in some ways analogous to treating advanced tuberculosis with a single drug; even with the much more selective anti-tuberculous drugs resistance will develop in some cases. This problem of a brief response to a single agent followed by resistance led to the introduction of combination chemotherapy. This was first applied by Li *et al.*, (1960) in testicular tumours and since then has expanded rapidly. The impact of combination regimes in acute lymphoblastic leukaemia is shown in Table V, and in carcinoma of the breast in Table VI. In the more drug-sensitive tumours this approach is now leading to apparent "cures" (patients dying of non-cancer causes with the same incidence as age-matched controls) in a proportion of patients (Table VII). One of the more dramatic advances in therapy has been the introduction of the MOPP (mustine, vincristine, procarbazine and prednisone) regime in advanced Hodgkin's disease (Devita *et al.*, 1970). Table VIII illustrates the complete remission rates with each of the four agents used singly, contrasted with the four drugs used in combination. Even more impressive than the complete remission rate is the median duration of complete remissions: with single agents it was three months, while with MOPP it was 36 months. A complete response is an important factor in prognosis in several tumours treated with chemotherapy. It is not altogether surprising that complete responders should do better than those who only respond partially, but this can be reflected directly in the pattern of survival. One example is given in a recent review of malignant teratomas (Samuels *et al.*, 1976) where the partial responders only did a little better than the non-responders while there was a markedly better prognosis in the complete responders.

The main accepted principles for selecting drugs in combination chemotherapy are shown in Table IX. It is important that the successes illustrated in Tables V, VI and VIII should not lead to premature use of combinations of drugs which have not been evaluated as single agents in particular tumours. There is still a range of tumours where most of the current agents have not been adequately assessed,

TABLE X

RECOGNIZED MECHANISMS OF RESISTANCE TO ANTI-CANCER DRUGS

Mechanism	Example
Defective transport of drug into cell	Methotrexate
Insufficient activation of a drug	Fluorouracil
Increased inactivation of a drug	Cytosine arabinoside
Increased or altered target enzyme	Methotrexate
Increased utilisation of alternative biochemical pathways	Antimetabolites
Increased repair of drug-induced damage	Alkylating agents

such as hypernephromas and carcinomas of the oesophagus, bladder and prostate. It is essential to have adequate data on the individual drugs before moving on to combinations of drugs.

In addition to proven activity when used alone, there are more theoretical considerations such as multiple metabolic blockades which may be induced by drug combinations (Fig. 2). Sequential, concurrent and complementary inhibition can lead to synergistic anti-tumour activity (Sartorelli and Creasey, 1969). There is always the problem of translating the *in vitro* data to the *in vivo* situation. One example is the use of thioguanine and cytosine arabinoside in L1210 leukaemia. *In vitro* they are less than additive, but *in vivo* they are synergistic (Schmidt *et al.*, 1970).

The problem of drug resistance is very important clinically. Although consistent and dramatic responses can be obtained in a range of tumours presenting with advanced disease, resistance can develop with varying rapidity in some of them. Carcinoma of the breast is a good example where the median duration of response to combination chemotherapy is still only around nine months with a wide range of drug combinations (Carter 1976). The resistance occurs not only to the agents that the cells have already been exposed to, but also to other drugs which are known to be active in that particular disease. The spectrum of resistance can become increasingly broad in carcinoma of the breast until the disease is completely drug resistant. This problem occurs not only in the relatively drug-sensitive tumours such as carcinoma of the breast, but is also seen in the very drug-sensitive tumours such as choriocarcinoma and acute lymphoblastic leukaemia. Drug resistance is the commonest cause of death in choriocarcinoma (Bagshawe 1976). How much of the resistance is due to altered tumour cell kinetics and how much is due to pharmacological resistance is unknown at present. Some of the recognized reasons for pharmacological drug resistance are shown in Table X.

The central nervous system (CNS) poses a special problem since many cancer chemotherapeutic agents have poor penetration into it. This has resulted in relapses occurring in the CNS in the leukaemias and in some solid tumours, while the disease elsewhere is under control. While some anti-cancer drugs have reasonable penetration into the CNS (the nitrosoureas, procarbazine and fluorourcil) other methods such as cranial irradiation and/or intrathecal therapy may be necessary to avoid this problem. Methotrexate, cytosine arabinoside and thiotepa can all be given intrathecally.

Adjuvant chemotherapy—The concept of adjuvant chemotherapy has become very important. When cancer is clinically detectable the disease is already advanced and there are good theoretical and experimental reasons for starting chemotherapy immediately after reduction of the bulk disease has been accomplished by local treatment. Schabel (1976; 1977) has recently reviewed the experimental evidence which shows that in a number of animal tumours a combination of chemotherapy and surgery can cure the majority of animals while either treatment alone is ineffective.

One of the main principles of adjuvant chemotherapy is that there should be a high risk of relapse following local treatment. Micrometastases are more likely to be responsive to chemotherapy since they have a high growth fraction (a high proportion of the tumour cell population dividing all the time), good drug access, a low concentration of competitive metabolites and less chance of developing drug resistance. Because there is no clinically detectable disease, only drugs and drug combinations which have been shown to be effective in advanced disease should be used. This concept has been applied for some years in selected tumours. The results with Wilm's tumours have been dramatic. From a five year survival of 16–23% with surgery and radiotherapy alone (Klapproth, 1959), Farber (1966) showed that by using actinomycin D for two years following surgery (with radiotherapy locally as necessary) 80% of this group are apparently long-term cures. More recent results suggest that for Stage I, II and III, the cure rate is going to be close to 100% (D'Angio *et al.*, 1976). Ewing's sarcoma may also be curable in a majority of cases presenting with localized disease and treated with adjuvant combination chemotherapy (Rosen *et al.*, 1974; Pomeroy and Johnson 1975). In these series about

70% of patients are remaining disease free. Embryonal rhabdomyosarcoma may also be curable in the majority of patients when local treatment is followed by adjuvant combination chemotherapy (reviewed by Burchenal, 1977).

Local treatment alone for osteosarcoma leads to 80% of patients developing pulmonary metastases at eighteen months. There are now several studies which show that adjuvant chemotherapy can apparently salvage 50–60% of patients rather than the 20% surviving after local treatment. These series have recently been reviewed (Burchenal, 1976; Jaffe, 1972; Jaffe *et al.*, 1977). Therapy with vincristine, high-dose methotrexate with folinic acid rescue, and in some cases with the addition of adriamycin, may be successful in altering the natural history of this disease.

Carcinoma of the breast is the commonest cause of death from cancer in women. It is known that 80% of patients with axillary nodes involved at the time of surgery (Stage II disease) will develop a recurrence at some time. There are now two major studies showing that recurrences can at least be retarded using adjuvant chemotherapy. Fisher *et al.* (1975) used melphalan as a single agent and Bonadonna *et al.* (1976) used a combination of cyclophosphamide, methotrexate and fluorouracil. One interesting feature of both these studies is that the pre-menopausal women do better with adjuvant chemotherapy than the post-menopausal ones. This has led to the suggestion, for which there is supporting evidence, that the chemotherapy is inducing a chemical oophorectomy (Rose and Davis, 1977). The paradox this evidence does not answer is why post-menopausal women with advanced breast cancer respond well to the same chemotherapy. With the long natural history of this disease, all that can be said so far is that adjuvant chemotherapy retards recurrences mainly in the pre-menopausal groups but it is too soon to know whether this will be reflected in an improved survival. Adjuvant chemotherapy in breast cancer is still an experimental approach and it is imperative that studies of this therapy continue to be properly randomized controlled trials (with an untreated control group) so that in due course a clear-cut answer as to the role of adjuvant chemotherapy in Stage II breast cancer will be available.

MONITORING THERAPY

It is self evident that in any form of therapy and, in particular, with cancer chemotherapy, the results of treatment should be adequately monitored. Although it has obvious limitations, clinical examination may be the only measurement available. Once a preliminary assessment suggests that a particular therapy is effective, properly designed clinical trials are necessary to confirm this. Historical controls are not adequate for this in most cases, as there has been a slow improvement in survival with many tumours over the last twenty years which cannot be readily identified with a single therapeutic change (Cutler *et al.*, 1975). On the other hand, the strict application of clinical trials in rapidly lethal cancers, before pilot studies have shown promising results, in fact retards clinical progress by limiting the number of therapeutic approaches that can be tried. Therefore there is a role both for the uncontrolled limited exploratory study and later for more formal clinical trials.

In assessing drug response the crudeness of clinical examination is rapidly apparent. The most commonly accepted definitions of response are:

Complete response. Disappearance of all tumour for a minimum period (usually a month or longer).

Partial response. A greater than 50% reduction in measurable disease (usually for a month or longer).

Stable and progressive disease—are self explanatory.

The monitoring of therapy would be much easier if there were a specific tumour product which accurately reflected the tumour bulk. The main uses of such a tumour product are shown in Table XI. There are already several tumour products in clinical use for monitoring certain tumours. These include human chorionic gonadotrophin (hCG) in choriocarcinoma and teratomas; alpha-fetoprotein (AFP) in malignant teratomas, Teilum's tumour, malignant hepatomas and in some gastrointestinal tract tumours; carcinoembryonic antigen (CEA) mainly in colonic carcinoma (although the CEA level in advanced disease does not correlate well with the clinical assessment). An example of how tumour products can be used is shown in Fig. 3. While in this case the hCG level gave a very useful guide to the success of chemotherapy, once the concentration

TABLE XI

USES OF TUMOUR-ASSOCIATED PRODUCTS

1.	Diagnosis and screening
2.	Monitoring complete or incomplete removal
3.	Early diagnosis of relapse
4.	Monitoring response to therapy
5.	Tumour localization

of hCG fell below that detectable in the assay the therapy was once more "blind". There can be anything up to about 10^6 tumour cells left at this stage, and the duration of treatment has to be an approximate projection of the slope of falling hCG to the point where there are zero cells. This is indicated in Fig. 3 by the question mark. It would be a great advantage to have a tumour product like this in the more common tumours. However it should be emphasized that being able to monitor the response

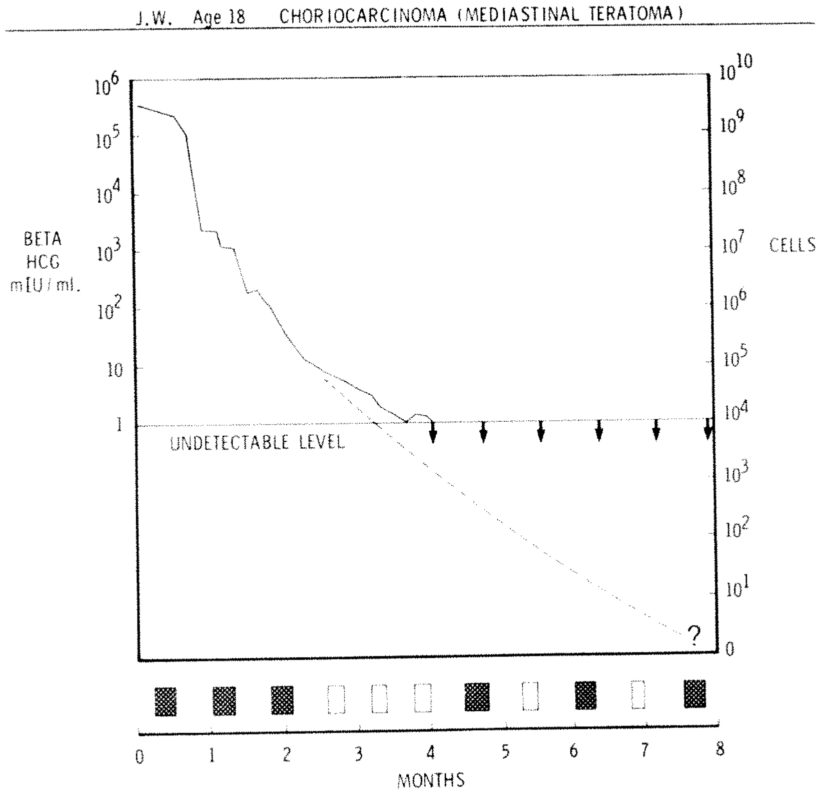


FIG. 3.

The use of a tumour marker, human chorionic gonadotrophin (HCG), in monitoring the response to therapy. The concentration of HCG is shown on the left and an estimate of the total number of tumour cells present is indicated on the right. Courses of multiple drug treatment are shown as rectangles below the abscissa. The arrows indicate undetectable levels of HCG.

Shaded rectangles: Hydroxyurea, Vincristine, Methotrexate, Cyclophosphamide, Actinomycin D, Adriamycin, Melphalan. Unshaded rectangles: Vinoblastine, Bleomycin infusion.

TABLE XII

CANCERS IN WHICH RESPONDING PATIENTS HAVE HAD AN IMPROVED SURVIVAL AS A RESULT OF CHEMOTHERAPY

Breast carcinoma
Ovarian carcinoma
Acute myeloid leukaemia
Multiple myeloma
Prostatic cancer
Lymphocytic lymphomas
Osteosarcomas

TABLE XIII

CANCERS IN WHICH RESPONSES TO CHEMOTHERAPY OCCUR BUT CLINICALLY USEFUL IMPROVEMENT IN SURVIVAL OF RESPONDERS HAS NOT BEEN CLEARLY DEMONSTRATED

Gastric carcinoma
Colonic carcinoma
Head and neck cancer
Primary C.N.S. tumours
Malignant melanoma
Carcinoma of Bronchus
Soft-tissue sarcomas
Bladder cancer
Pancreatic cancer
Hepatomas
Thyroid cancer
Neuroblastoma

of a tumour product does not make the tumour drug sensitive. While choriocarcinoma is drug sensitive, and therapy is directly influenced by the rate of hCG fall, a comparable assay in a drug-resistant tumour such as advanced colonic cancer would speed the screening of inactive drugs, but would not necessarily alter the management until effective agents became available.

Clinical Impact of Cancer Chemotherapy

The rapid progress in cancer chemotherapy over the last twenty years has affected certain selected tumours more than others, and the types of tumour that are most drug sensitive are relatively rare. Table VII shows the tumours in which chemotherapy results in a varying proportion of patients achieving a normal life span. This small group of aggressive tumours accounts for approximately 7% of all cancers. The next group (Table XII) of tumours is more common, accounting for some 25% of all cancers. The responding patients in this category have an improved survival on chemotherapy. The third group (Table III), representing about 50% of all cancers, do respond to some extent to chemotherapy, but this so far has made only a minor impact on survival. There is a further miscellaneous group of tumours in which chemotherapy has either not been evaluated at all, or which have failed to respond to the drugs which have been studied. This may appear less impressive, but it should be remembered that until the last few years interest had been limited to a selected group of tumours: there are large areas which have not been adequately studied. In no tumours in the four groups indicated above have all the current 30 to 40 agents been completely assessed, and in a number of tumours almost no evaluation of single agent drugs has yet been done. It will probably take at least another five years before all the gaps in our knowledge of the range of anti-tumour activity of each of the current agents have been filled. It will take even longer to learn how best to combine and schedule the range of active drugs which would then be available. In the meantime, of course, it is hoped that more selective agents will have been found. A further note of caution is necessary: practically all the current cytotoxic agents are also carcinogenic in animals. With improved survival, second tumours are being detected with increasing frequency in cancer patients (Harris 1976, Sieber 1976). In those patients treated with cytotoxic agents, the main second tumour so far has been the development of acute myeloid leukaemia in patients treated with long-term alkylating agent therapy for multiple myeloma and carcinoma of the ovary. There is, as yet, no evidence that the high-dose pulsed therapy which is now used is as carcinogenic as the former low-dose continuous administration. However, the long-term complications of chemotherapy will have to be carefully monitored.

Local treatment for cancer may still improve the control of local disease further. At present it seems likely that the impact of surgery alone is reaching a plateau in its effect on survival of cancer patients. The role of radiotherapy may improve rather more in that newer forms of radiation such as neutron therapy and the current interest in radiosensitizers may in due course significantly improve local control. However far both these local treatments may improve, this will leave a majority of patients who die from cancer being killed by metastatic disease. Clearly the major improvement in cancer therapy has got to be further radical and it is hoped rapid improvement in systemic treatment. While further basic research into the process of malignant transformation continues, and the search for more selective anti-cancer drugs goes on, there is a great deal that can be done with the three current modalities of treatment. The optimum combination of surgery, radiotherapy and chemotherapy should be able to alter the natural history of an increasing range of tumours over the next few years.

REFERENCES

Bagshawe, K. D., Magrath, I. T., and Golding, P. K., 1969. Intrathecal Methotrexate. *Lancet*, *2*, 1258.

Bagshawe, K. D., 1976. Treatment of trophoblastic tumours. *Annals of the Academy of Medicine of Singapore*, *5*, 273.

Bayard, S., Greenberg, R., Showalter, D., and Byar, D., 1974. Comparison of treatments for prostatic cancer using an exponential-type life model relating survival to concomitant information. *Cancer Chemotherapy Reports*, *58*, 845.

Benesch, K. G., and Malawista, S. E., 1969. Microtubular crystals in mammalian cells. *The Journal of Cell Biology*, *40*, 95.

Blackard, C. E., Doe, R. P., Mellinger, G. T., and Byer, D. P., 1970. Incidence of cardiovascular disease in patients receiving diethylstilboestrol for carcinoma of the prostate. *Cancer*, *26*, 249.

Bloom, H. J. G., 1972. Renal Cancer. *Endocrine Therapy of Malignant disease*. Edited by B. A. Stoll, p. 339 (W. B. Saunders and Company).

Bonadonna, G., Brusamolino, E., Valagussa, P., and Rossi, A., 1976. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *New England Journal of Medicine*, *294*, 405.

Bruce, W. R., Meeker, B. E., and Valeriote, F. A., 1966. A comparison of the sensitivity of normal hematopoietic and transplanted lymphoma colony forming cells to chemotherapeutic agents administered *in vivo*. *Journal of the National Cancer Institute*, *37*, 233.

Burchenal, J. H., 1976. Adjuvant chemotherapy—theory, practice and potential. The James Ewing Lecture. *Cancer*, *37*, 46.

1977. Adjuvant therapy—an exciting milestone. *Recent Advances in Cancer Treatment*, *3*, 121.

Carter, S. K., 1976. Integration of chemotherapy into combined modality treatment of solid tumours. VII Adenocarcinoma of the breast. *Cancer treatment Reviews, 3,* 141.

Chabner, B. A., Myers, C. E., Coleman, C. N., and Johns, D. G., 1975. The clinical pharmacology of antineoplastic agents. *New England Journal of Medicine, 292,* 1107 and 1159.

Connors, T. A., Cox, P. J., Farmer, P. B., Foster, A. B., and Jarman, M., 1974. Some studies of the active intermediates formed in the microsomal metabolism of cyclophosphamide and isophosphamide. *Biochemical Pharmacology, 23,* 115.

Connors, T. A., 1975. Drugs used in the treatment of cancer. *FEBS Letters 57,* 223.

Cutler, S. J., Myer;, M. H., and Green, S. B., 1975. Trends in survival rates of patients with cancer. *New England Journal of Medicine, 293,* 122.

D'Angio, G. J., Evans, A. E., Breslow, N., Beckwith, B., Bishop, H., Feigl, P., Goodwin, W., Leape, L., Sinks, L., Sutow, W., Trefft, M., and Wolff, J., 1976. The treatment of Wilms' Tumor. Results of the national Wilms' tumor study. *Cancer, 38,* 633.

Devita, V. T., Serpick, A. A., and Carbonne, P. P., 1970. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Annals of Internal Medicine, 73,* 881.

Devita, V. T., Young, R. C., and Canellos, G. P., 1975. Combination versus single agent chemotherapy: a review of the basis for selection of drug treatment of cancer. *Cancer, 35,* 98.

Di Marco, A., Gaetani, M., and Scarpinato, B., 1969. Adriamycin: a new antibiotic with anti-tumour activity. *Cancer Chemotherapy Reports, 53,* 33.

Duschinsky, R., Pleven, E., and Heidelburger, C., 1957. The synthesis of 5-Fluoro-pyrimidines. *Journal of American Chemical Society, 79,* 4559.

Farber, S., 1966. Chemotherapy in the treatment of leukaemia and Wilms' tumour. *Journal of the American Medical Association, 198,* 826.

Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J., 1948. Temporary remission in acute leukaemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (Aminopterin). *New England Journal of Medicine, 238,* 787.

Fisher, B., Carbonne, P., Economou, S. G., Frelick, R., Glass, A., Lerner, H., Redmond, C., Zelen, M., Band, P., Katrych, L., Wolmark, N., and Fisher, E. R., 1975. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. *New England Journal of Medicine, 292,* 117.

Frei, E., 1974. *Effect of dose and schedule on response in Cancer Medicine.* Edited by J. F. Holland and E. Frei. p. 717 (Lea and Febiger).

Furth, J. J., and Cohen, S. S., 1968. Inhibition of mammalian DNA polymerase by the 5′-triphosphate of 1-B-D-arabinofuranosylcytosine and the 5′-triphosphate of 9-B-D-arabinofuranosyl adenine. *Cancer Research, 28,* 2061.

Gilman, A., and Phillips, F. S., 1946. The biological actions and therapeutic applications of the B-chlorethylamines and sulphides. *Science, 103,* 409.

Harris, C. C., 1976. The carcinogenicity of anticancer drugs: a hazard in man. *Cancer, 37,* 1014.

Horwitz, S. B., and Loike, J. D., 1977. A comparison of the mechanism of action of VP16-213 and Podophyllotoxin. *Lloydia, 40,* 82.

Huggins, C., and Hodges, C. V., 1941. Studies on prostatic cancer; effect of castration of oestrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Research, 1,* 293.

Jaffe, N., 1972. Recent advances in the chemotherapy of metastatic osteogenic sarcoma. *Cancer, 30,* 1627.

Jaffe, N., Traggis, D., Cassady, J. R., Filler, R. M., Watts, H., and Frei, E. III. 1977. *Recent advances in Cancer Treatment,* Edited by H. J. Tagnon and M. J. Staquet, *3,* 291.

Johnston, J. P., McCaleb, G. S., and Montgomery, J. A., 1963. The synthesis of antineoplastic agents—XXXII N-Nitrosoureas. *Journal of Medicinal Chemistry,* 6, 669.

Kelly, R. M., and Baker, W. H., 1961. Progestational agents in the treatment of carcinoma of the endometrium. *New England Journal of Medicine, 264,* 216.

Kidd, J. G., 1953. Regression of transplanted lymphomas implanted *in vivo* by means of normal guinea pig serum. *Journal of Experimental Medicine, 98,* 565.

Klapproth, H. J., 1959. Wilm's tumour: a report of 45 cases and an analysis of 1,351 cases reported in the world literature from 1940–1958. *Journal of Urology, 81,* 663.

Lefrak, E. A., Pitha, J., Rosenheim, S., and Gottlieb, J. A., 1973. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer, 32,* 302.

Levitt, M., Mosher, M. B., DeConti, D., Farber, L. R., Skeel, R. T., Marsh, J. C., Mitchell, M. S., Papac, R. J., Thomas, E. D., and Bertino, J. R., 1973. Improved therapeutic index of Methotrexate with Leucovorin rescue. *Cancer Research, 33,* 1729.

Li, M. C., Whitmore, W. F., Golbey, R., and Grabstald, H., 1960. Effects of combined drug therapy on metastatic cancer of the testis. *Journal of the American Medical Association, 174,* 1291.

McGuire, W. L., Carbonne, P. P., Sears, M. E., and Escher, G. C., 1975. *Estrogen Receptors In Human Breast Cancer.* Edited by W. L. McGuire, P. P. Carbonne and E. P. Vollmer, (Raven Press, New York).

Mellett, L. B., 1972. Considerations in the design of optimal therapeutic schedules, pharmacology and the future of man. *Problems of Therapy,* edited by G. T. Okita and G. H. Acheson, published by S. Karger, p. 332.

Mitchley, B. C. V., Clarke, S. A., Connors, T. A., and Neville, M. A., 1975. Hexamethylmelamine-induced regression of human lung tumours growing in immune-deprived mice. *Cancer Research, 35,* 1099.

Pigram, W. J., Fuller, W., and Hamilton, L. D., 1972. Stereochemistry of intercalation: interaction of daunomycin with DNA. *Nature New Biology, 235,* 17.

Pitman, S. W., Parker, M., Tattersall, M. H. N., Jaffe, N., and Frei, E. III, 1975. Clinical trials of high-dose Methotrexate-Citrovorum factor, toxicological and therapeutic observations. *Cancer Chemotherapy Reports, 6* 43.

Pomeroy, T. C., and Johnson, J. E., 1975. Combined modality therapy of Ewing's Sarcoma. *Cancer, 35,* 36.

Rose, D. P., and Davis, T. E., 1977. Ovarian function in patients receiving adjuvant chemotherapy for breast cancer. *Lancet, 1,* 1174.

Rosen, G., Wollner, N., Tan, C., Wu, J., Hajdu, S. I., Cham, W., D'Angio, G. J., and Murphy, M. L., 1974. Disease-free survival in children with Ewing's sarcoma treated with radiation therapy and adjuvant four-drug sequential chemotherapy. *Cancer, 33,* 384.

Rosenberg, V., Van Camp, L., and Krigas, T., 1965. Inhibition of cell division in *E. coli* by electrolysis products from a platinum electrode. *Nature, 205,* 698.

Rozencweig, M., Von Hoff, D. D., Slavik, M., and Muggia, F. M., 1977a. Dis-diamminedichloroplatinum II: a new anti-cancer drug. *Annals of Internal Medicine, 86,* 803.

Rozencweig, M., Von Hoff, D. D., Henney, J. E., and Muggia, F. M., 1977b. VM-26 and VP16-213: a comparative analysis. *Cancer, 40,* 334.

Samuels, M. L., Lanzotti, V. J., Holoye, P. Y., Boyle, L. E., Smith, T. L., and Johnson, D. E , 1976. Combination chemotherapy in germinal cell tumours. *Cancer Treatment Reviews, 3,* 185.

Sartorelli, A. C., and Creasey, W. A., 1969. Cancer chemotherapy. *Annual Review of Pharmacology, 9,* 51.

Schabel, F. M., 1975. Synergism and antagonism among antitumour agents. in *Pharmacological Basis of Cancer Chemotherapy*, p. 595 (Williams and Wilkins Company).

1976. Concepts for treatment of micrometastases developed in murine systems. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 126*, 500.

1977. Experimental basis for adjuvant chemotherapy. *Adjuvant Therapy of Cancer.* Edited by S. S. Salmon and S. E. Jones, p. 3 (North-Holland).

Schmidt, L. H., Montgomery, J. A., Laster, W. R., and Schabel, F. M., 1970. Combination therapy with arabinosylcytosine and thioguanine. *Proceedings of the American Association of Cancer Research, 11*, 70.

Sieber, S. M., 1976. Cancer chemotherapeutic agents and carcinogenesis. *Cancer Chemotherapy Reports, 59*, 915.

Skipper, H. E., Schabel, F. M., and Wilcox, W. S., 1967. Experimental evaluation of potential anticancer agents XXI. Scheduling of arabinosylcytosine to take advantage of its s-phase specificity against leukaemia cells. *Cancer Chemotherapy Reports, 51*, 125.

Suzuki, M., Nagai, K., Yamaki, H., Tanaka, N., and Umezawa, H., 1968. Mechanism of action of bleomycin. Studies with growing cultures of bacteria and tumour cells. *Journal of Antibiotics* (*A*), *21*, 379.

Tattersall, M. H. N., 1975. Anticancer drugs: pharmacology and drug interactions. *Clinical Oncology, 1*, 223.

Tattersall, M. H. N., Sodergren, J. E., Sengupta, S. K., Trites, D. H., Modest, E. J., and Frei, E. III, 1975. Pharmacokinetics of actinomycin D in patients with malignant melanoma. *Clinical Pharmacology and Therapeutics, 17*, 701.

Tattersall, M. H. N., Jarman, M., Newlands, E. S., Holyhead, L., Milstead, R. A. V., and Weinberg, A., 1978. Pharmacokinetics of melphalan following oral or intravenous administration. *European Journal of Cancer, 14*, 507.

Umezawa, H., Maeda, K., Takeuchi, T., and Okami, Y., 1966. New antibiotics bleomycin A and B. *Journal of Antibiotics*, (*Tokyo*), *19*, 200.

Wasserman, T. H., Comis, R. L., Goldsmith, M., Handelsman, H., Penta, J. S., Slavik, M., Soper, W. T., and Carter, S. K., 1975. Tabular analysis of the clinical chemotherapy of solid tumours. *Cancer Chemotherapy Reports, 6*, 399.

Book review

Obstetrical Diagnosis by Radiographic, Ultrasonic and Nuclear Methods. Edited by J. A. Campbell. Golden's Diagnostic Radiology, pp. xi+202, illus., 1977 (Williams & Wilkins Company, Baltimore). $29.00.

Professor J. A. Campbell has edited a thoroughly revised edition of the obstetrics volume in the Golden's Diagnostic Radiology tome. Not only has the section on X-ray applications been updated but there are new sections on isotope and ultrasonic diagnosis, of which the latter is, properly, predominant. It is a generously illustrated book which aims to integrate the various imaging modalities and offers problem orientated advice on the ordering of tests and their relative usefulness. It is comprehensive, with very good coverage of the commoner obstetric conditions and venturing some way with rarer disorders especially in the radiology of fetal skeletal abnormalities. It is primarily a radiologist's text, but contains much that should be of interest to obstetricians. There are good modern reference lists and a comprehensive index.

Over half the book is X-ray work, beginning with a section on hazards to the fetus, which is really the only section one feels constrained to take issue with since it approaches the problem by way of minimizing it. The opening comment "The curtailment of the use of diagnostic X-rays, based on the fear of possible radiation injury, have been largely confined to obstetrical radiology" sets the tone. This is not as generally true in Europe as apparently in the U.S.A. The conclusion of this chapter "The hazards of antenatal radiography are of such small order of magnitude as to be clinically acceptable wherever there is a clear indication for such examinations" of course begs the whole question. Radiological techniques are covered with emphasis on special devices to increase the information obtained from a single exposure (double screens, etc.) and then a section on normal gestations with criteria for assessing maturity. Fetal and gestational abnormalities are thoroughly covered and there is an especially clear chapter on contrast studies, both fetal and uterine. Maternal adaptations to pregnancy and associated diseases are allocated further separate chapters. All of these are profusely illustrated, but sadly many of the radiographs are difficult to make out, a well known but frustrating effect of printing.

A brief but aposite discussion of the physics of diagnostic ultrasound introduces a chapter in which the major applications are well covered, although it is quite rightly assumed that scanning techniques are to be learned at the bedside and not from a text book. The findings in normal pregnancy are carefully outlined with good discussion of cephalometry including criteria, reasons for error, accuracy rates and their clinical usefulness. Abnormal gestations are illustrated and discussed and in general the ultrasound tomogram reproductions seem to have suffered less in printing than the radiographs, although quite a number are still in the outmoded bistable system—one now expects to see grey scale images exclusively. The use of ultrasound in directed amniocentesis is mentioned.

A short final chapter deals with the use of radioisotopes in placental localization; with extreme good grace it points out that this method is of historical interest now, having been eclipsed by ultrasonic localization.

Where conventional X-ray techniques are used in obstetrical diagnosis, this book will be invaluable for its detailed and comprehensive coverage. The ultrasound section is a little too brief to recommend as the definitive reference work.

David O. Cosgrove.

1978, *British Journal of Radiology*, *51*, 771–781

OCTOBER 1978

Orbitocranial asymmetry

By E. H. Burrows, M.Rad., F.R.C.R.

Department of Neuroradiology, Wessex Neurological Centre, Southampton General Hospital,
Southampton SO9 4XY

(*Received May, 1977*)

ABSTRACT

Eleven cases are chosen to illustrate the differential diagnosis of deforming lesions of the bony orbit and its vicinity, which cause unilateral proptosis or other craniofacial disfigurement. Three distinct varieties of orbitocranial neurofibromatosis are distinguished, and they are contrasted with other deforming lesions of childhood—unilateral craniosynostosis, chronic juvenile subdural hygroma of the temporal fossa and congenital facial hemihypertrophy. Adult lesions are represented by intrinsic tumours of the orbit and paranasal sinuses, and by the commonest two processes deforming the sphenoid bone, meningioma and osseous fibrous dysplasia.

Orbitocranial lesions are rare and they are usually diagnosed by their radiological appearances. A variety of unrelated conditions deform and erode the bony orbit and adjacent cranium, producing remarkably uniform clinical pictures yet radiological features which may be distinctive.

CASE REPORTS

The following 11 cases were selected to illustrate the radiological differential diagnosis of orbitocranial asymmetry. The clinical feature common to all of them was a unilateral proptosis or other clinical disfigurement due to deformity of the skeleton in the vicinity of one eye, for which the patient or his parents sought medical advice. The radiological features of these patients are given in Table I. Radiographs of the bony orbits are shown in Fig. 1.

Case 1

A three-year-old boy with a puffy left eye and expanded left temple, which had been present since birth. No defect of vision but orbital deformity prompted the parents to press for surgical treatment. *Plain radiographs* (*Figs.* 1A *and 2*): hypertrophy of the left orbit and optic canal, a bulging temporal fossa and a J-shaped sella, but contrast studies failed to confirm the presence of a chiasmal mass. Operative exploration: tentacle-like structures occupied the roof of the orbital cavity and blended posteriorly with the fascia and dura; there was no discrete mass. No sphenoid ridge was present. The left optic nerve and chiasm when exposed were shown to be normal and not invaded by tumour. Diagnosis: generalized neurofibromatosis (plexiform neuroma of the orbit and sphenoid dysplasia).

Case 2

A 20-year-old girl complaining of defective vision. Family history of generalized neurofibromatosis. Physical

TABLE I

RADIOLOGICAL SIGNS—STRUCTURES AFFECTED

Case (age)	Orbital rim	Optic canal	Sphenoid wing	J sella	Temporal fossa	Diagnosis
1. T.G. (3)	+	− +	+	+	+	Generalized neurofibromatosis (PNO+SD)
2. D.M. (20)	+	+ +	−	+	−	Generalized neurofibromatosis (OG only)
3. T.T. (7)	+	− −	+	−	−	Generalized neurofibromatosis (SD only)
4. S.M. (11)	−	− −	+	−	+	Chronic juvenile subdural hygroma
5. S.S. (8)	−	− −	+	−	−	Plagiocephalic craniostenosis
6. S.G. (8)	+	− −	−	−	+	Facial hemihypertrophy
7. N.S. (11)	+	− +	+	−	−	Eyeball enucleation (retinoblastoma)
8. L.K. (26)	+	− −	−	−	−	Orbital epidermoid
9. D.R. (12)	+	− +	+	−	−	Fibrous dysplasia of bone
10. J.A. (54)	−	+ −	+	−	−	Sphenoid meningioma
11. D.B. (65)	+	− −	−	−	−	Frontal sinus mucocoele

OG=optic glioma. PNO=plexiform neuroma of the orbit. SD=sphenoid defect.

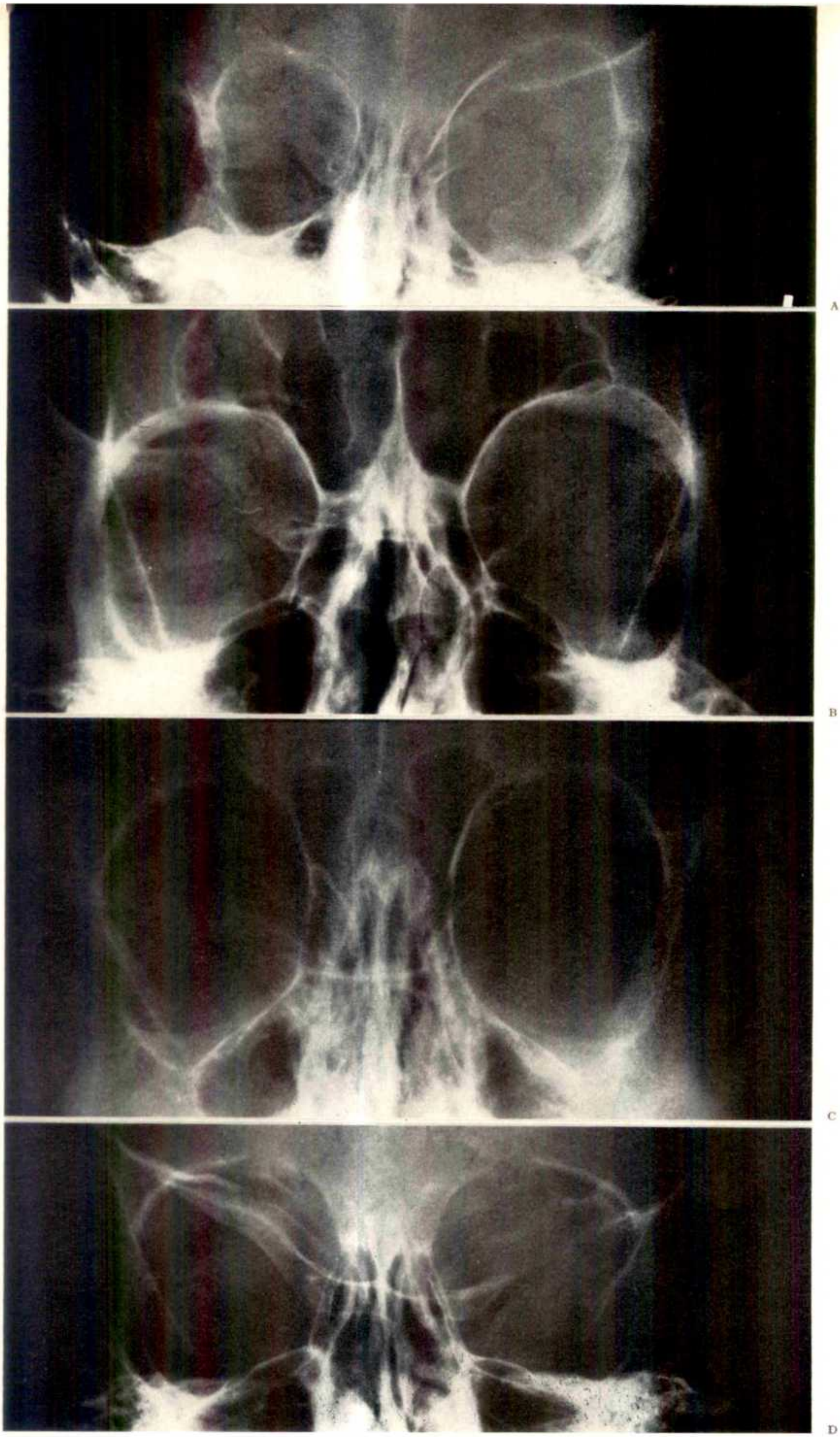


FIG. 1.

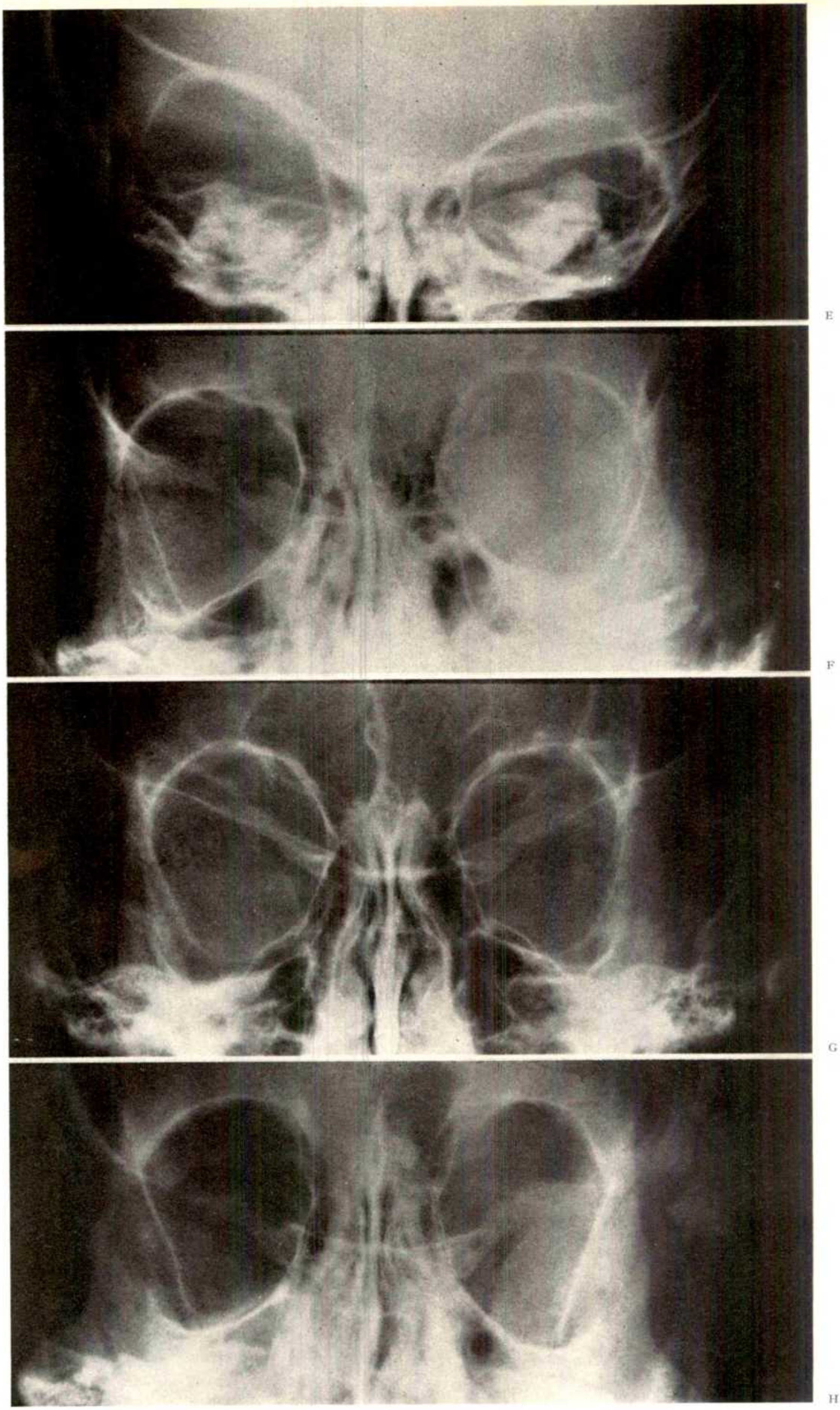


FIG. 1.

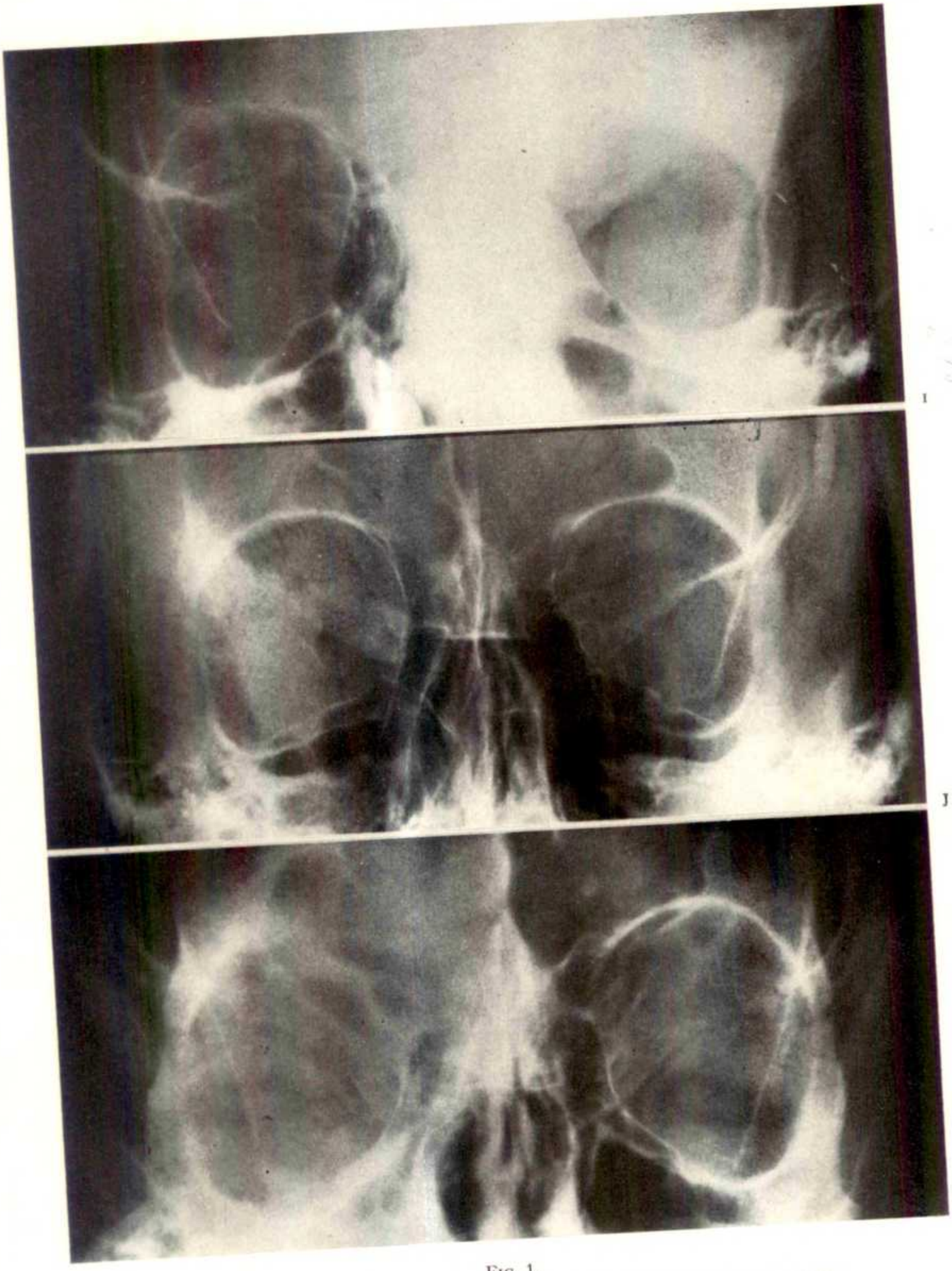


FIG. 1.

Orbital margins of cases 1–11. For clinical and radiological details, see case reports.

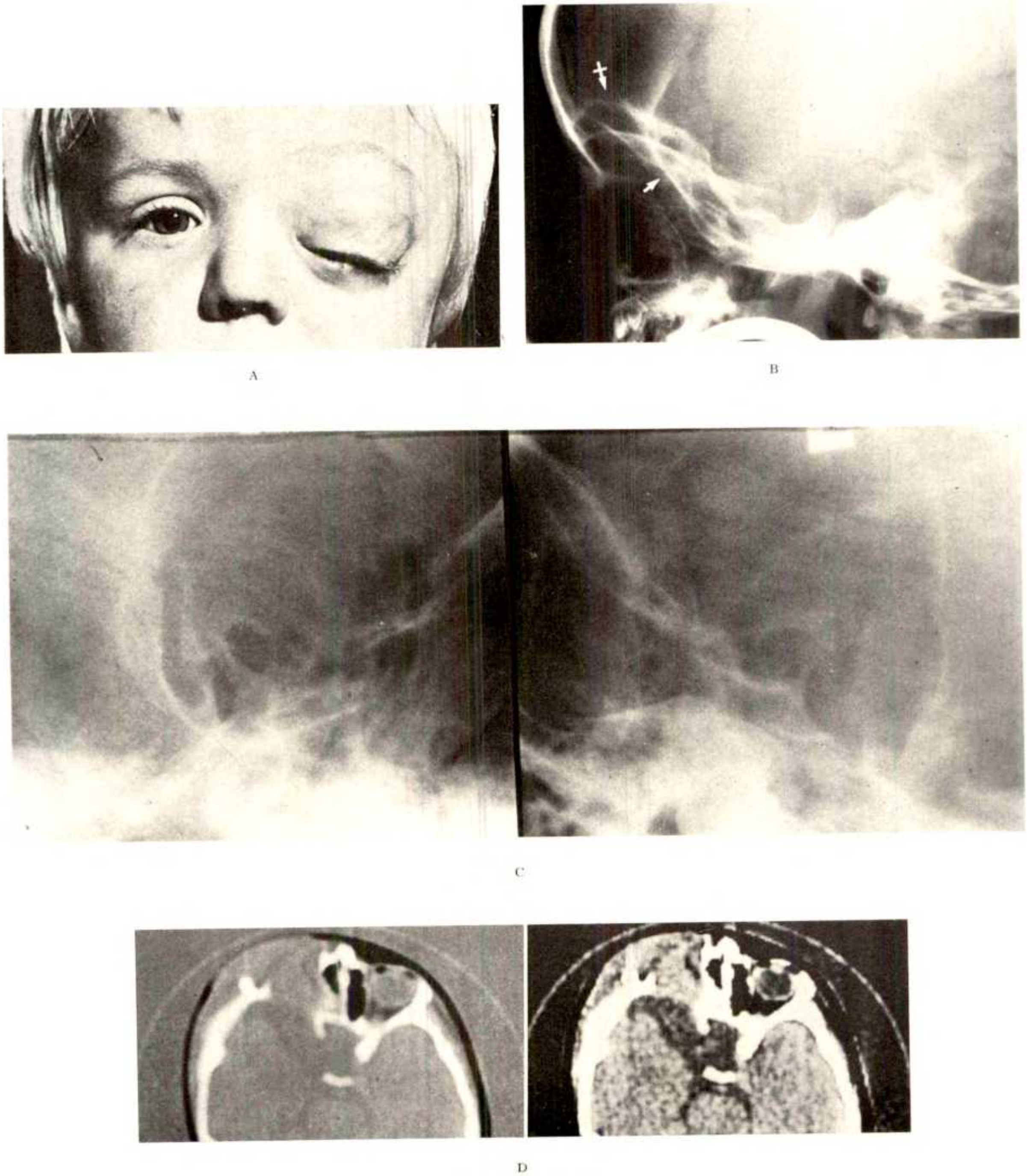


FIG. 2. *Case 1.*

Orbital neurofibromatosis.

(A) Appearance at age of three years.

(B) Lateral view showing J-shaped pituitary fossa, bulging temporal fossa (↗) and large orbit (↓).

(C) Hypertrophied left orbit and optic canal.

(D) CT scan: axial view showing the bulging temporal fossa and defective sphenoid wing. The left eyeball has been displaced from view by the soft tissue mass, which is being compressed into the orbital cavity by the head holder of the scanner.

SITY COLLEGE LIBRARY

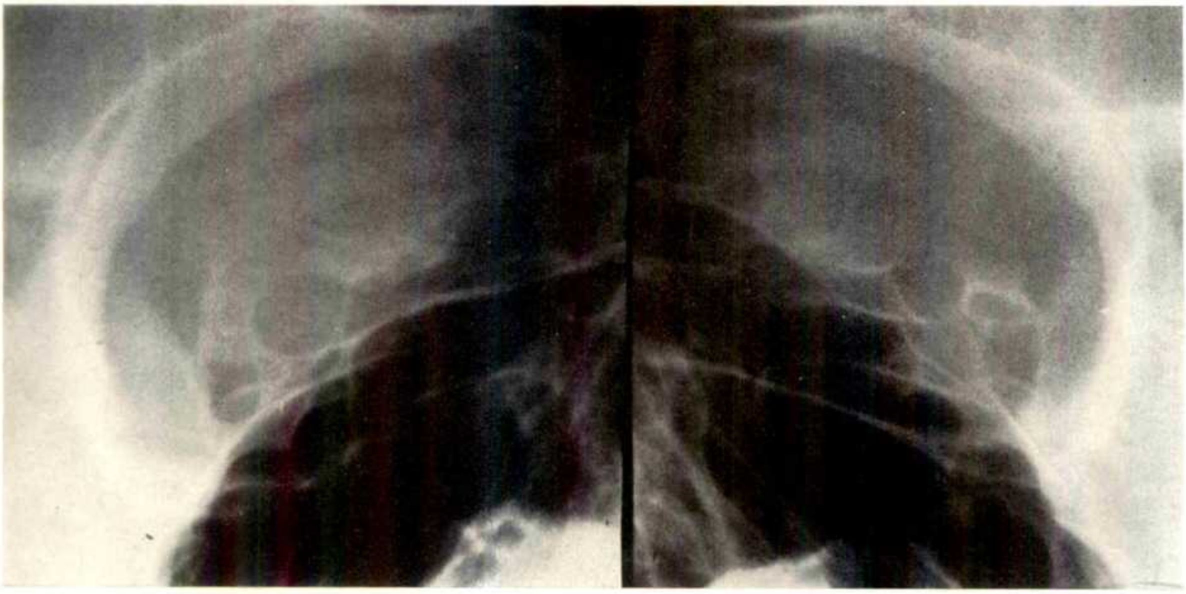


Fig. 3. *Case 2.*

Glioma of the anterior optic pathway in a patient with generalized neurofibromatosis. Optic canal views: both canals have lost their cortical lining. The right canal is about twice the normal size and the left canal also is probably abnormally large.

examination revealed bilateral optic atrophy, slight left proptosis and cutaneous signs of generalized neurofibromatosis. *Plain radiographs* (*Figs. 1*B *and 3*): enlargement of the left orbit and probably of the left optic canal, also of the right optic canal, and pneumoencephalography outlined a chiasmal mass. Surgically unconfirmed but blind eight years later. Diagnosis: generalized neurofibromatosis (optic glioma involving chiasm and both nerves).

Case 3

A seven-year-old boy with a prominent left eye since birth, which pulsates when he becomes excited. The patient and his father exhibited cutaneous features of generalized neurofibromatosis. *Plain radiographs* (*Fig. 1*C): left bony orbit slightly enlarged, sphenoid wing elevated and innominate line displaced outwards. However, clinical and radiological examinations revealed no evidence of an orbital or chiasmal tumour, and surgical exploration was not advised. Diagnosis: generalized neurofibromatosis (sphenoid defect).

Case 4

An 11-year-old boy found upon examination after a minor accident, to have a bulging right temporal fossa. *Plain radiographs* (*Figs. 1*D *and 4*): right sphenoid wing elevated and innominate line displaced laterally but orbital margin not enlarged, temporal fossa grossly expanded. Past history: caesarean birth, convulsions as a baby, a lump noticed on the right of the head at the age of six years. Right carotid angiography confirmed the presence of an extradural collection covering the temporal lobe and occupying the expanded area of the middle cranial fossa. Asymptomatic, and no surgical treatment indicated. Diagnosis: chronic juvenile subdural hygroma.

Case 5

An eight-year-old boy with a marked right proptosis and deformity of the forehead, which had been present since infancy. *Plain radiographs* (*Fig. 1*E): typical "harlequin" appearance of right bony orbit, caused by unilateral synostosis of the coronal suture, which tethers the sphenoid wing. No operation advised. Diagnosis: hemicoronal synostosis (plagiocephaly).

Case 6

An eight-year-old boy under the care of a maxillofacial surgeon, with a swelling of the left cheek and face since infancy. Histological confirmation of the congenital lesion, namely hypertrophy of the mesodermal tissues, mostly lymphangiomatous material, was obtained in the course of several operations on the tissues and skeleton, which were aimed at removing excessive growth. *Plain radiographs* (*Fig. 1*F): hemihypertrophy of the facial skeleton and soft tissues. The effect of the skeletal changes was to elevate the left bony orbit. Unexplained intracranial calcification visible beneath rim of the left orbit. Diagnosis: congenital facial hemihypertrophy, unexplained intracranial calcification.

Case 7

An 11-year-old boy referred for the investigation of vague intracranial symptoms. At the age of 3½ years his left eyeball had been excised for retinoblastoma. Physical examination revealed a distorted face, due to the smaller left eye. *Plain radiographs* (*Figs. 1*G *and 5*): significantly smaller left bony orbit (vertical diameter 5.2 cm, compared with right orbit 5.7 cm). Sphenoid wing and optic canal proportionately reduced in size. Diagnosis: failure of normal growth of bony orbit and optic canal, due to childhood enucleation.

Case 8

A 26-year-old prospective bride whose fiancé told her to get her eye "fixed up" before marriage. For the past six months she had been aware of deformity of the left eye and examination revealed the eyeball to be prominent and displaced downwards, with a firm mobile mass palpable above it (Fig. 6). A scar was present from a ptosis operation performed at the age of nine years. A presumptive diagnosis was made of mucocoele of the frontal sinuses, or perhaps a

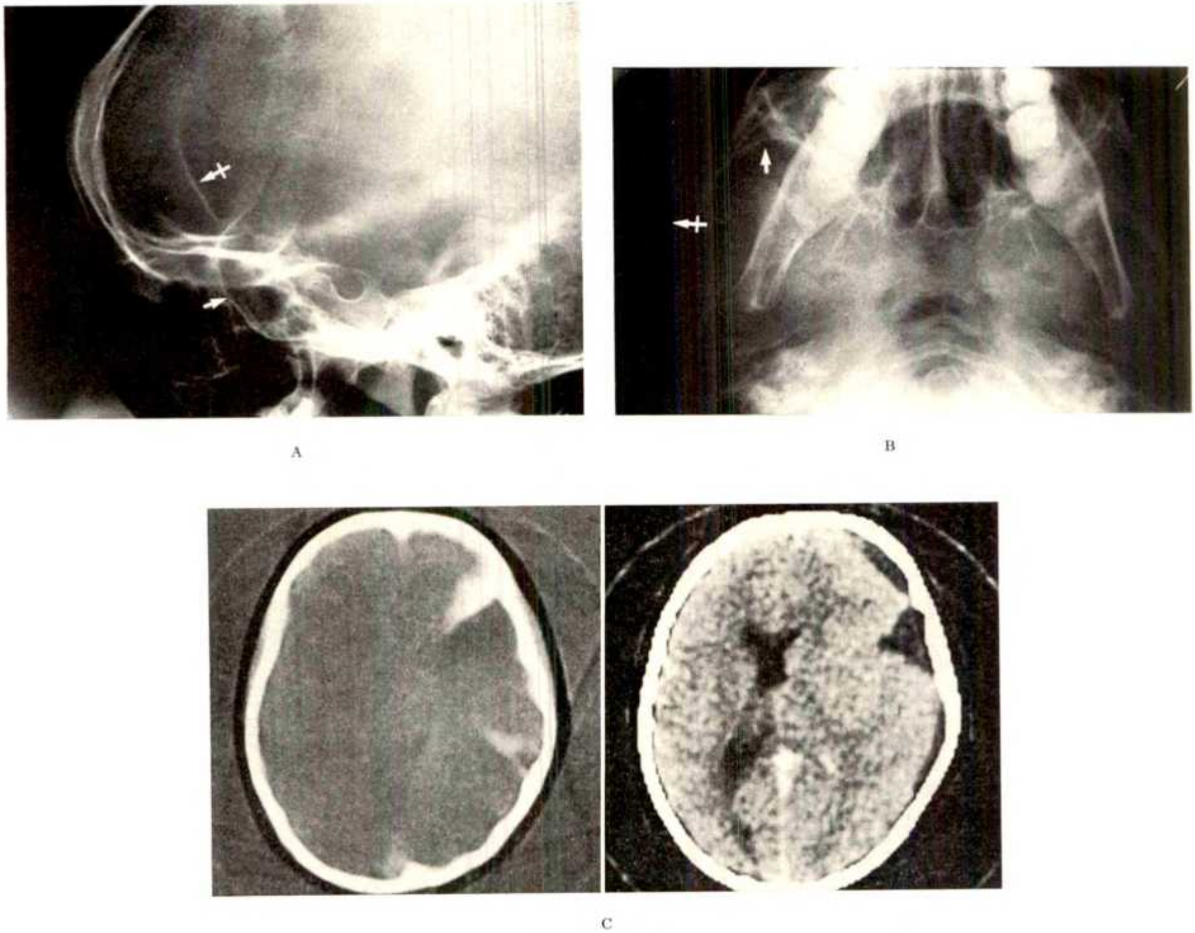


FIG. 4. *Case 4.*

Chronic juvenile subdural hygroma of temporal fossa. (A) and (B) Lateral and submentovertical views showing forward-bulging sphenoid wing (↗) and anterior limit of thinned, bulging temporal squame (←+).
(c) CT scan, showing elevated sphenoid wing with fluid collection beneath it and extending over the hemispherical convexity. It was thicker over the vertex, accounting for the significant midline displacement.

foreign body reaction associated with the previous operation. *Plain radiographs* (*Fig. 1*H): focal pressure erosion of the bony orbit but no destruction. Operative diagnosis: pearly tumour (epidermoid).

Case 9

A 12-year-old boy with bony deformity of the left side of the forehead and left proptosis. No visual defect but diplopia on upward gaze. *Plain radiographs* (*Fig. 1*I): extensive deformity of the left orbit including its margin and contents by osseous fibrous dysplasia, which also involves the sphenoid body and frontal squame. The left optic canal is reduced to about half its normal diameter. Diagnosis: fibrous dysplasia of bone.

Case 10

A 54-year-old woman who complained of a painless but progressive right proptosis (Fig.7). *Plain radiographs and CT Scan* (*Fig. 1*J *and* 7B)*:* Extensive thickening of the right sphenoid wing typical of an *en plaque* meningioma. Optic canal constricted by surrounding meningioma. Diagnosis: sphenoid meningioma.

Case 11

A 65-year-old woman complained of facial pain and swelling of the right orbit for several years. *Plain radiographs* (*Fig. 1*K)*:* destruction of the superomedial segment of the right bony orbit, and sclerosis of the right frontal sinus. Opacity of right frontal, ethmoidal and maxillary sinuses. Operative diagnosis: mucocoele.

RADIOLOGICAL FEATURES

(a) *Deformed orbital rim*

Several types of orbitocranial dislocation deform the rim of one bony orbit, producing an obvious asymmetry. Enucleation of the eyeball in early life and certain skeletal affections such as osseous fibrous dysplasia result in a small and deformed orbit, and radiological examination illuminates the diagnosis (Fig. 1G and I). Equally characteristic may be the radiological appearances of neoplastic

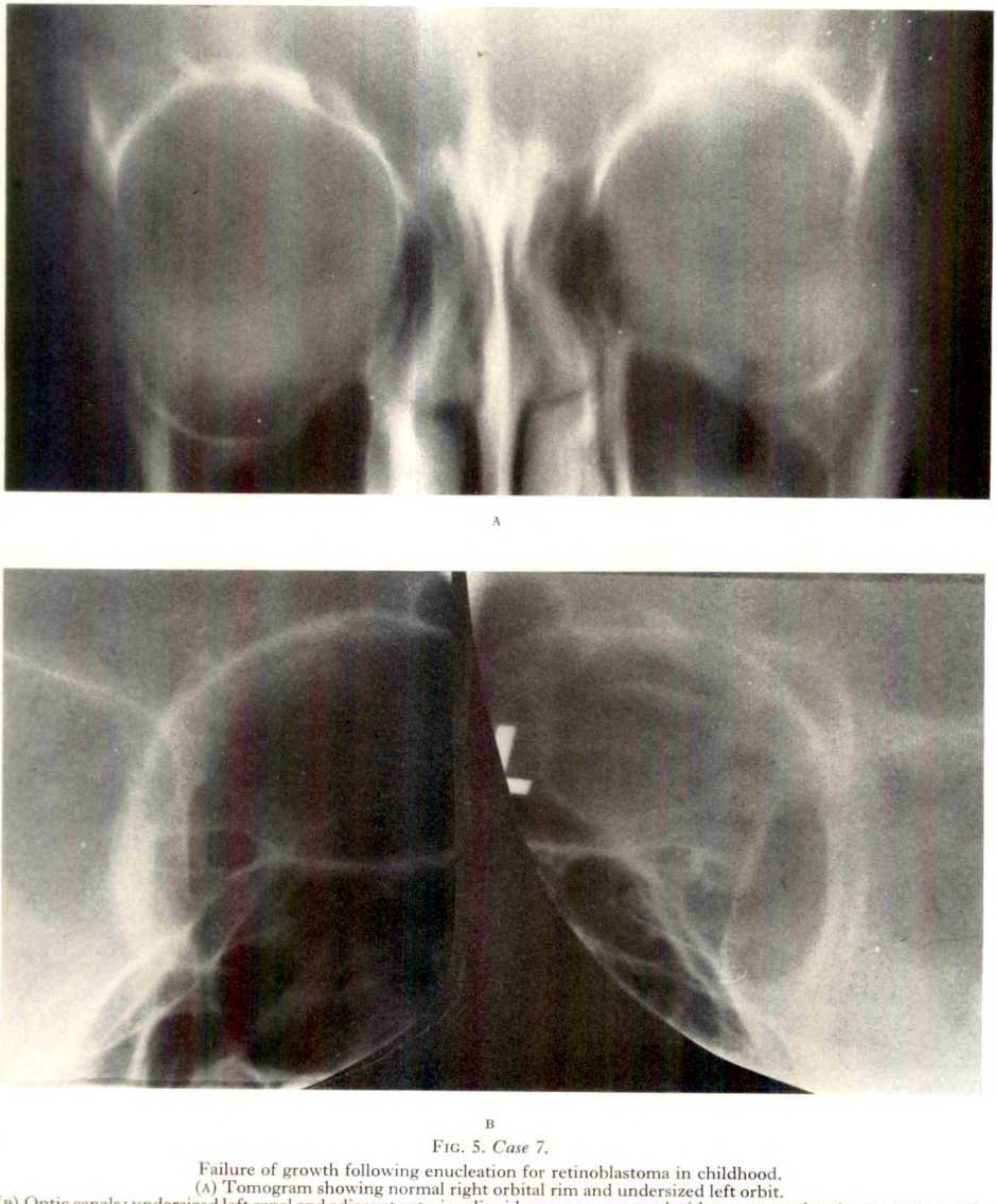


FIG. 5. *Case 7.*

Failure of growth following enucleation for retinoblastoma in childhood.
(A) Tomogram showing normal right orbital rim and undersized left orbit.
(B) Optic canals: undersized left canal and adjacent anterior clinoid process, compared with structures showing normal growth on the opposite side.

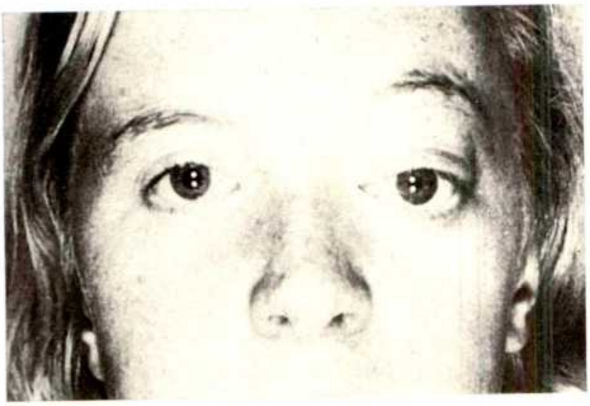
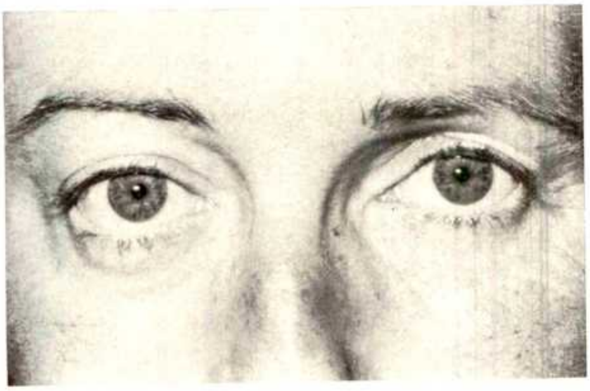
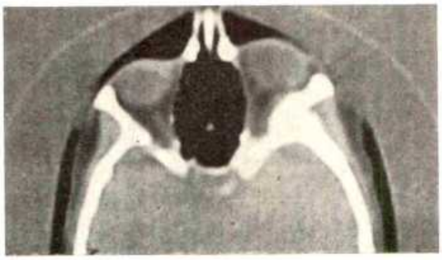


FIG. 6. *Case 8.*
Orbital epidermoid.



A



B

FIG. 7.

Meningioma of sphenoid wing.

(A) Right proptosis.

(B) CT scan: axial view of orbits and cranial bones showing the right eyeball displaced forwards and slightly downwards by thickening of the entire greater and lesser right sphenoid wings, including the anterior clinoid process. Structures displaced within the orbital cavity include, apart from the eyeball itself, the lateral rectus muscle and optic nerve.

deposits or a mucocoele of the paranasal sinuses, which destroy parts of the orbital rim (Fig. 1K).

Orbital enlargement denotes a benign lesion of the bony orbit which is of long standing (Lloyd, 1967). However, this rule does not apply in children, in whom raised intraorbital pressure more quickly enlarges it. A distinction must be drawn between symmetrical and asymmetrical enlargement. Symmetrical *i.e.* almost geometric, enlargement points to a tumour within the muscle cone, causing an even distribution of intraorbital pressure *e.g.* glioma of the optic nerve (Case 2, Fig. 1B). Tumours outside the muscle cone tend to produce asymmetrical enlargement of the orbital rim, sometimes with focal erosion, indentation and bone reaction of the wall adjacent to the mass, *e.g.* epidermoid (Case 8, Fig. 1H). Intraorbital tumours that enlarge the bony orbit without eroding it seldom deform intraorbital structures such as the oblique line and sphenoid ridge; however, the optic canal may be enlarged through spread of a retinoblastoma to involve the intracanalicular part of the optic nerve.

In orbital neurofibromatosis enlargement of the rim of the bony orbit may accompany any one of three separate lesions. From study of 23 personal cases of orbital neurofibromatosis, it is clear that each mechanism may, by itself, enlarge the orbit. The 13 instances of orbital hypertrophy in the 23 cases were distributed as follows: (1) sphenoid dysplasia alone—four out of five cases; (2) optic glioma alone—one out of ten; (3) plexiform neuroma of the orbit—five out of five; (4) combined lesions (sphenoid dysplasia and plexiform neuroma)—three out of three. These findings confirm that orbital enlargement almost invariably accompanies sphenoid dysplasia (Evans *et al.*, 1963; Binet *et al.*, 1969) and that this deformity is uncommon in cases of solitary optic glioma. The presence of sphenoid dysplasia may be difficult to verify, even by exploratory craniotomy, and enlargement of the bony orbit combined with enlargement of the optic canal should always raise the suspicion of generalized neurofibromatosis (Burrows, 1963).

Hemicoronal synostosis (plagiocephalic craniostenosis) enlarges the bony orbit by distorting it, the outer and upper corner being drawn up towards the tethered coronal suture—the so-called "harlequin" deformity (Case 5, Fig. 1E).

Another rare cause of an asymmetrical bony orbit is congenital facial hemihypertrophy. The extent of the hypertrophy in this condition varies greatly, yet it can be diagnosed instantly by radiography (Campbell, 1971). It may resemble fibrous dysplasia of bone, but orbital enlargement is unusual in fibrous dysplasia (Leeds and Seaman, 1962). If the hemihypertrophy includes the eyeball or orbital soft tissues, the result is a proptotic eye in an enlarged bony orbit. However, if the orbital contents are spared, the bony orbit may escape deformity and merely be displaced upwards as part of the hemifacial skeletal overgrowth. Orbital radiographs show it lying at a higher level than normal (Case 6, Fig. 1F).

(b) *Enlarged optic canal*

Enlargement of the optic canal in orbitocranial asymmetry is limited to those conditions which produce hypertrophy of the bony orbit. For practical purposes, the combination of orbital hypertrophy and uniform widening of the optic canal is limited to generalized neurofibromatosis and optic glioma; very rarely, space-occupying lesions of the orbital cavity invade the sheath of the optic nerve and enlarge the canal *e.g.* retinoblastoma. About one quarter of optic gliomas are encountered in patients with generalized neurofibromatosis (Marshall, 1954).

A non-neoplastic cause of enlargement of the optic canal in this disease should always be questioned: Dresner and Montgomery (1949) failed to find a single instance in 49 cases with optic atrophy. However, in a patient described here (Case 1), the plexiform neurofibroma extending backwards in the orbit actually blended with the thickened orbital fascia and dura and replaced the defective sphenoid wing, without involving the optic canal, which was enlarged radiographically (Fig. 2c). Orbitofrontal craniotomy was carried out and it showed the optic chiasm and nerves to be normal. The enlarged optic canal was therefore assumed to be part of the general hypertrophy of the contents of the orbit, secondary either to the sphenoid dysplasia or the plexiform neuroma, or both. In Case 2 the grossly enlarged right optic canal was caused by a glioma of the optic chiasm extending through the foramen to involve the intraorbital part of the nerve and in this way enlarging the orbit.

(c) *Abnormal sphenoid wing*

The spectrum of sphenoid wing changes in orbitocranial asymmetry in generalized neurofibromatosis includes the following: elevated lesser sphenoid wing, laterally-displaced innominate line, hypoplastic or absent greater sphenoid wing, absent optic canal. If the orbit is enlarged, the greater sphenoid wing is usually displaced forwards as well. The actual combination of radiological features found in each case depends upon the cause of the deformity. The sphenoid dysplasia is thought to be the result of an underdevelopment of the growth centres of the sphenoid bone (Binet *et al.*, 1969). Cases 1 and 3 are the typical variations of this disease. Rarely, the only radiological finding is congenital absence of the superior orbital wall (Lewald, 1933; Burrows, 1963). More usually, sphenoid dysplasia is accompanied by an enlarged orbit (Case 3).

Changes of the sphenoid wing in two other lesions mimic generalized neurofibromatosis—chronic juvenile subdural hygroma of the temporal fossa and unilateral synostosis of the coronal suture (plagiocephaly). In temporal hygromas (see below), a bulging middle cranial fossa deforms the sphenoid wings by displacing them forwards and upwards, and the innominate line outwards—producing a "bare orbit" identical to that of neurofibromatosis; but the orbital margin is never enlarged. In hemicoronal synostosis, a condition in which the patient usually presents at a much younger age, premature closure of one side of the coronal suture has a tethering effect, so that the lesser sphenoid wing, as well as the superolateral quadrant of the orbit, are elevated. The innominate line is prolonged upwards (Case 5, Fig. 1E).

Circumscribed sclerotic changes in the sphenoid bone are usually caused by meningioma, osseous fibrous dysplasia and, rarely, osteoblastic metastases. The radiological differential diagnosis may be difficult: sphenoid meningiomas tend to exhibit an eccentric growth pattern and invade either a greater wing or lesser wing, then both, before involving the planum sphenoidale (Figs. 1J and 7B). Conversely, in fibrous dysplasia the mid-line is almost always involved extensively if the sphenoid wings are affected (Fig. 1I).

(d) *So-called J sella*

This term is a misnomer. Although in lateral view the deformity appears to be a forward extension of the pituitary fossa (converting it into a J- or omega shape), it actually represents an anatomical deformity of the upper surface of the sphenoid bone (Martin and Cushing, 1923). The J sella is a feature of gliomas of the anterior optic pathway including those that occur in cases of generalized neurofibromatosis, but it is also seen in such unconnected conditions as chronic low-grade hydrocephalus, achondroplasia and gargoylism. Very occasionally, it is found as part of the sphenoid dysplasia of orbital neurofibromatosis without optic glioma *e.g.* Case 1 (Fig. 2B). Thus, the J-shaped sella—or some instances of this deformity—appears to be the result of an aberration of sphenoid growth—possibly faulty fusion of the pre-sphenoid and basisphenoidy segments (Burrows, 1964; Kier, 1966).

The differential diagnostic value of the J sella in orbitocranial asymmetry is obvious: a large proportion of cases of orbital neurofibromatosis show it, but none of the other conditions producing this deformity.

(e) *Bulging temporal fossa*

This particular feature of cranial asymmetry has been described in association with temporal arachnoid cysts which contain clear fluid. A link with childhood trauma is usually postulated or proved, either chronic subdural haematoma (Davidoff and Dyke, 1938; Bull, 1949) or chronic subdural hygroma (Hardman, 1939; Childe, 1953). Others have pointed out that the adjacent temporal lobe in such patients is underdeveloped (Tiberin and Gruszkiewicz, 1961), and for this reason Robinson (1964) suggested the name "temporal lobe agenesis syndrome" to replace all others. He defined the syndrome as "agenesis of the temporal lobe which is replaced by a collection of cerebrospinal fluid and the skull bulges over it".

The radiological features were well described by Bull (1949), namely a bulging and thinned temporal squame, elevated lesser sphenoid wing and laterally-displaced innominate line. Forward and outward bulging of the middle cranial fossa is best shown on lateral and full-axial views of the skull. A characteristic sign in the lateral view is the scalloped anterior edge of the thinned parietal squame (Fig. 4A).

A bulging temporal fossa may be present in orbital neurofibromatosis but there is an important difference. In neurofibromatosis deforming the middle fossa, the bony orbit is invariably enlarged, while in chronic subdural hygromas it is unaltered in size. Other very rare causes of temporal fossa enlargement are slow-growing, superficially situated gliomas in children (Jupe, 1938) and unilateral cerebral agenesis in infants (Childe, 1953). Case 6 was an instance of congenital hemihypertrophy in which a unilateral enlargement of the facial bones produced a local bulging of the temporal squame clinically and radiologically which mimicked that present in Cases 1 and 4.

ACKNOWLEDGMENT

Grateful thanks are expressed to Mr David Whitcher, medical photographer in the Teaching Media Department, University of Southampton for preparing the illustrations.

REFERENCES

Binet, E. F., Kieffer, S. A., Martin, S. H., and Peterson, H. O., 1969. Orbital dysplasia in neurofibromatosis. *Radiology*, *93*, 829–833.

Bull, J. W. D., 1949. The diagnosis of chronic subdural haematoma in children and adolescents. *British Journal of Radiology*, *22*, 68–80.

Burrows, E. H., 1963. Bone changes in orbital neurofibromatosis. *British Journal of Radiology*, *36*, 549–561.
1964. The so-called J-sella. *British Journal of Radiology*, *37*, 661–669.

Campbell, J. A., 1971. Craniofacial anomalies. In *Radiology of the skull and brain*, *1*, pp. 571–633 (Mosby, St Louis).

Childe, A. E., 1953. Localized thinning and enlargement of the cranium with special reference to the middle fossa. *American Journal of Roentgenology*, *70*, 1–22.

Davidoff, L. M., and Dyke, C. G., 1938. Relapsing juvenile chronic subdural haematoma: a clinical and roentgenographic study. *Bulletin of the Neurological Institute of New York*, *7*, 95–111.

Dresner, E., and Montgomery, D. A. D., 1949 Primary optic atrophy in Von Recklinghausen's disease. *Quarterly Journal of Medicine*, *18*, 93–103.

Evans, R. A., Schwartz, J. F., and Chutorian, A. M., 1963. Radiologic diagnosis in pediatric ophthalmology. *Radiologic Clinics of North America*, *1*, 459–495.

Hardman, J., 1939. Asymmetry of the skull in relation to subdural collections of fluid. *British Journal of Radiology*, *12*, 455–461.

Jupe, M. H., 1938. The reaction of the bones of the skull to intracranial lesions. *British Journal of Radiology*, *11*, 146–164.

Kier, E. L., 1966. Embryology of the normal optic canal and its anomalies. An anatomic and roentgenographic study. *Investigative Radiology*, *1*, 346–362.

Lewald, L. T., 1933. Congenital absence of the superior orbital wall associated with pulsating exophthalmos. *American Journal of Roentgenology*, *30*, 756–764.

Leeds, N., and Seaman, W. B., 1962. Fibrous dysplasia of the skull and its differential diagnosis. *Radiology*, *78*, 570–582.

Lloyd, G. A. S., 1967. Radiological signs in proptosis. *Transactions of the Ophthamological Society of the United Kingdom*, *87*, 375–383.

Marshall, D., 1954. Glioma of the optic nerve (as a manifestation of Von Recklinghausen's disease). *American Journal of Ophthalmology*, *37*, 15–36.

Martin, P., and Cushing, H., 1923. Primary gliomas of chiasm and optic nerves in their intracranial portion. *Archives of Ophthalmology*, *52*, 209–241.

Robinson, R. G., 1964. The temporal lobe agenesis syndrome. *Brain*, *87*, 87–106.

Tiberin, P., and Gruszkiewicz, J., 1961. Chronic arachnoidal cysts of the middle cranial fossa and their relation to trauma. *Journal of Neurology, Neurosurgery and Psychiatry*, *24*, 86–91.

1978, *British Journal of Radiology*, *51*, 782–787

Pseudopolyposis in Crohn's disease

By A. H. Freeman, M.B., F.R.C.R.,* F. R. Berridge, M.A., M.B., F.R.C.P., F.R.C.R.,*
A. P. Dick, M.A., M.D., F.R.C.P.,* J. A. Gleeson, M.B., M.R.C.P., F.R.C.R.,†
and R. Zeegen, M.B., M.R.C.P.†

Departments of Radiology and Medical Gastroenterology, Addenbrooke's Hospital, Cambridge,* and the Departments of Radiology and Gastroenterology, Westminster Hospital, London†

(*Received February, 1978*)

ABSTRACT

Eight cases of pseudopolyposis occurring in Crohn's colitis are described. Emphasis is placed on the variability of the lesions. Four of the cases demonstrate localized giant pseudopolyposis which has until recently been regarded mainly as a complication of ulcerative colitis.

Colonic pseudopolyposis occurring in Crohn's disease has received little attention in the radiological literature. Indeed at one time it was considered not to be a feature of this condition. Wolf and Marshak (1962) stress the distinction between the cobblestone mucosal pattern of Crohn's disease and pedunculated pseudopolyps, but considered that true pseudopolyps were rare in Crohn's disease. Of two major series comparing ulcerative and Crohn's colitis, Stanley *et al.* (1971) found no pseudopolyps in 32 patients with Crohn's disease, whereas Margulis *et al.* (1971) mentioned nine examples of pseudopolyposis out of 60 cases of granulomatous colitis, although they later emphasised the importance of pseudopolyposis as a roentgenographic sign of ulcerative colitis. Welin and Welin (1976) in their monograph on the double contrast barium enema discuss in detail the appearances of pseudopolyps in ulcerative colitis but do not comment on their presence in Crohn's disease.

Although it is now widely recognized that pseudopolyps do occur in Crohn's disease (Young, 1969; Marshak, 1975; Laufer, 1977) there has been remarkably little work published regarding their radiological appearances. A distinction between the two forms of pseudopolyposis has been made by Berridge (1975) who comments that pseudopolyps due to Crohn's disease are seldom seen at the first examination in an untreated patient and may appear after treatment with steroids.

Our attention was drawn to the matter by a case of localized giant pseudopolyposis which masqueraded as a villous tumour and presented with attacks of intestinal obstruction. There have been two case reports of this complication in Crohn's colitis

TABLE I

DETAILS OF CASES.

Case	Sex	Age	Duration	Extent of disease	Pseudopolyps		Pathological confirmation of Crohn's disease	Previous steroids
					Site	Type		
1. C.W.	M	53	1 year	Descending colon	Descending colon	1	Colectomy	No
2. A.M.	M	25	5 years	Right colon	Right colon	1	Colectomy	Yes
3. J.W.	M	30	9 years	Terminal ileum, caecum, ascending colon	Ascending colon	1	Colectomy	Yes
4. E.S.	M	53	6 years	Terminal ileum, whole colon	Sigmoid	2	Colectomy	Yes
5. L.B.	M	40	5 years	Terminal ileum, whole colon	Sigmoid	2	Colectomy	Yes
6. C.O.	F	60	10 years	Terminal ileum, whole colon	Whole colon	3	Colectomy	Yes
7. J.L.	M	34	12 years	Terminal ileum, caecum, ascending colon, recto-sigmoid	Ascending colon	4	None	Yes
8. E.P.	F	68	37 years	Whole colon	Sigmoid	4	Rectal biopsy	Yes

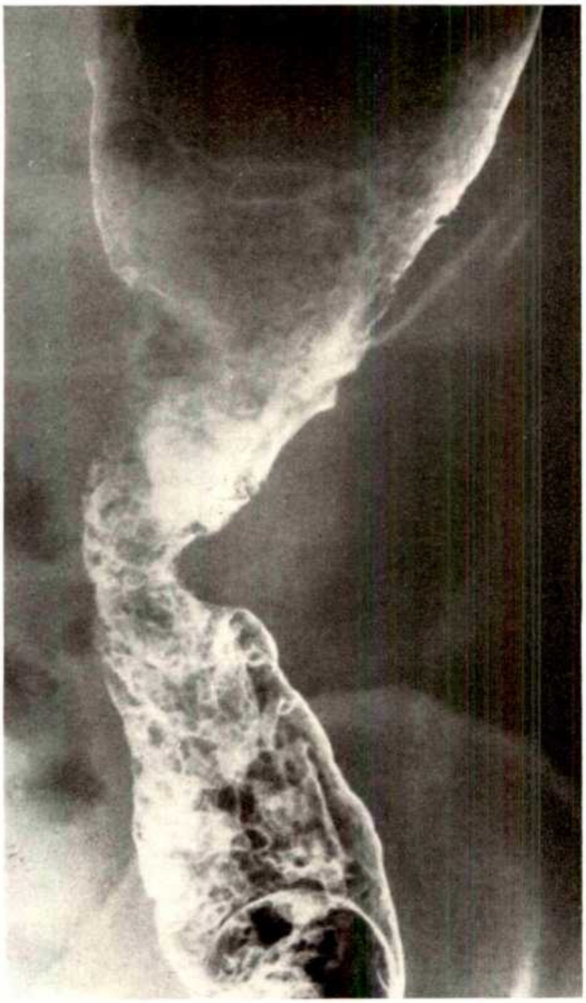


FIG. 1. *Case 1.*
Barium enema showing exuberant polyposis in the descending colon with a strictured area above. The proximal colon is distended.

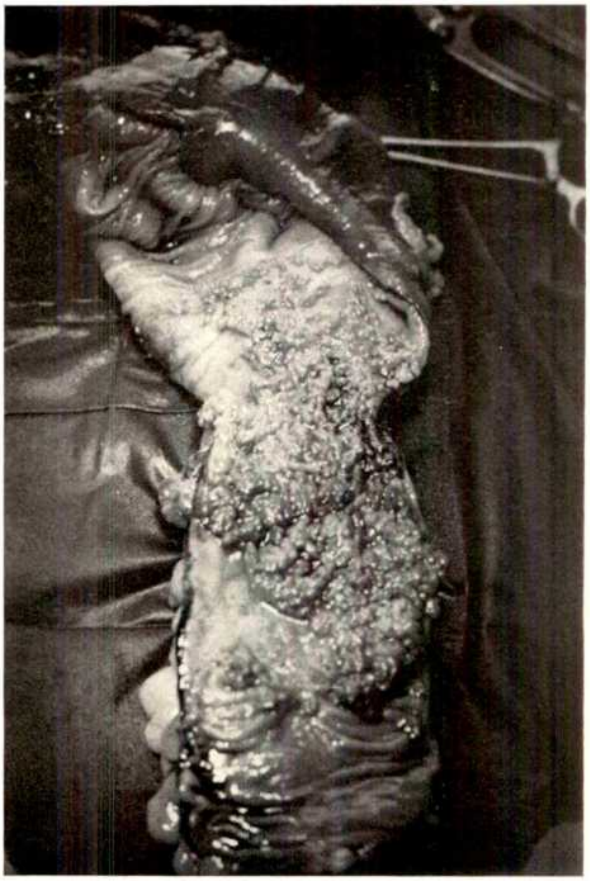


FIG. 2. *Case 1.*
Opened operative specimen confirming the massive pseudopolyposis.

(Schneider *et al.*, 1973; Wills and Han, 1977) and whilst this paper was being prepared two further reports (Joffe, 1977; Ayre-Smith, 1977) added three more cases, thus bringing the total number recorded to five. This of course is a well recognized complication of ulcerative colitis (Ferrucci, 1972; Hinrichs and Goldman, 1968).

We wish to report a series of cases which demonstrate the wide spectrum of appearances, apart from the not uncommon small mucosal lesion, that may

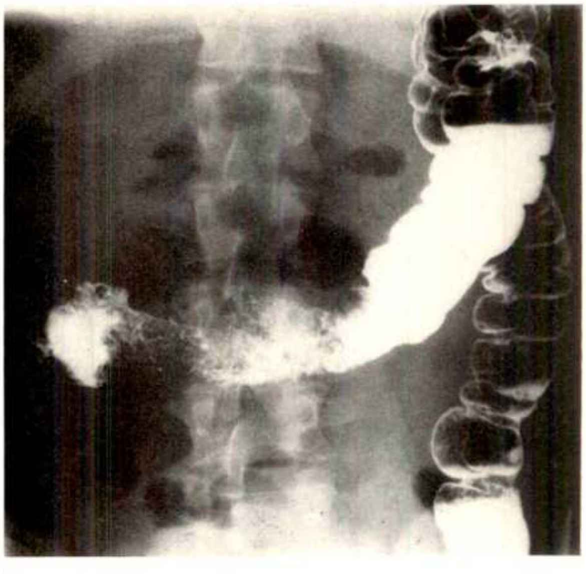


FIG. 3. *Case 2.*
Barium enema demonstrating complete obstruction in the proximal transverse colon due to a mass of pseudopolyps.

result from pseudopolyposis due to Crohn's disease of the colon.

PRESENT SERIES

These eight examples are drawn from a large number of patients with Crohn's disease seen in the gastroenterological departments of two hospitals.

We have divided the types of radiological abnormality found into the following:

(1) *Localized multiple pseudopolyposis*, *i.e.* large numbers of relatively small pseudopolyps in a segment of colon;

(2) *Localized giant pseudopolyposis*, *i.e.* a collection of larger pseudopolyps giving rise to a mass lesion within the colon;

(3) *Generalized pseudopolyposis;*

(4) *Long finger-like pseudopolyps.*

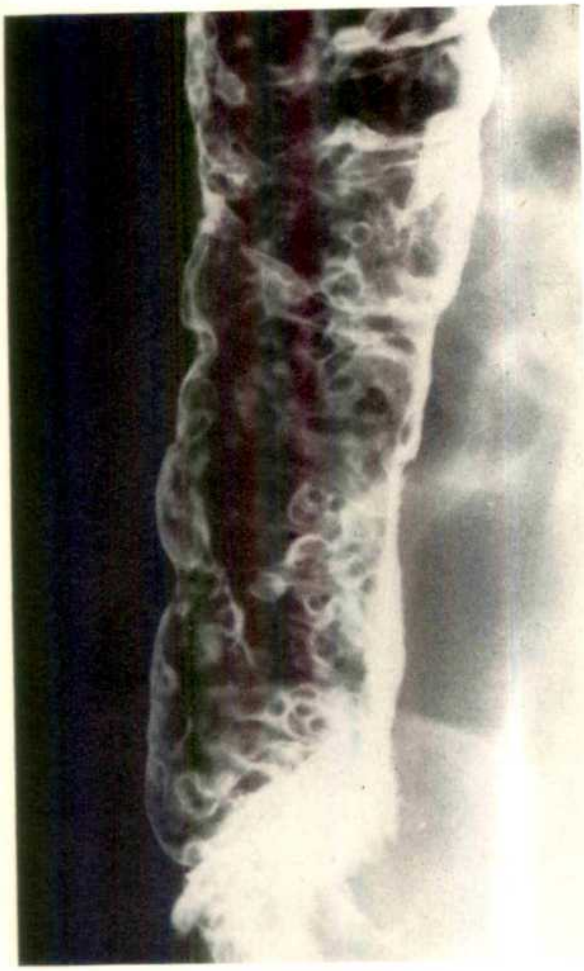


Fig. 4. *Case 3.*

Decubitus view of the ascending colon during a barium enema which shows multiple small discrete pseudopolyps.

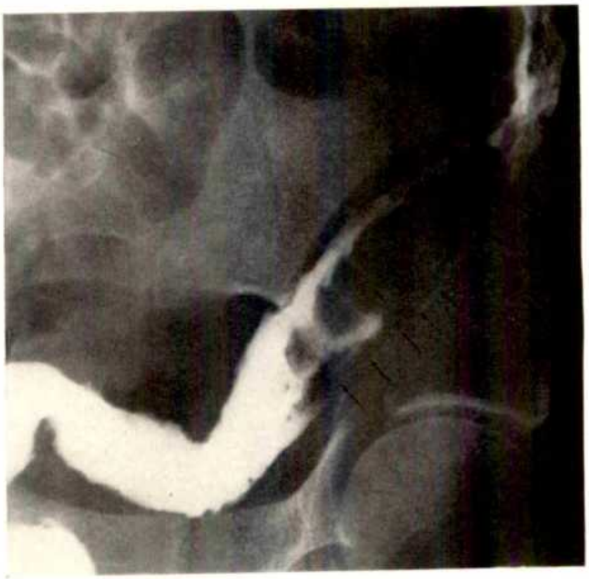


Fig. 5. *Case 4.*

Post-evacuation film of a barium enema showing large round and oval pseudopolyps in the sigmoid colon which occupy the whole lumen.

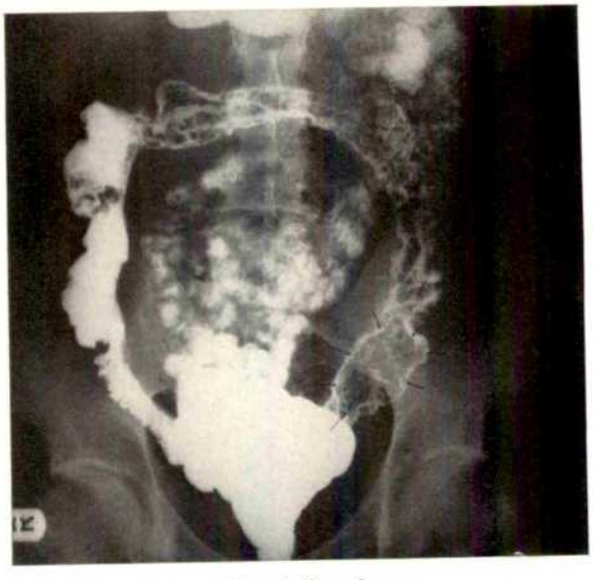


Fig. 6. *Case 5.*

Barium follow-through showing a collection of large pseudopolyps in the sigmoid colon which give rise to a mass lesion within the bowel.

Details of the cases at the time of the first barium study revealing pseudopolyposis are summarized in Table I. Pathological confirmation of the diagnosis of Crohn's disease was obtained in all patients except No. 7. This patient developed rectal bleeding and diarrhoea, and barium studies demonstrated extensive small bowel involvement with fistulae typical of Crohn's disease.

Type 1: Localized multiple pseudopolyposis

Three patients were seen with this type of change, that is to say that they had a large collection of small pseudopolyps, usually under 0.5 cm diameter, localized in a segment of colon. This type of appearance is usually referred to as "localized giant pseudopolyposis" and may be associated with obstructive symptoms. We prefer the term "localized multiple pseudopolyposis" because of their relatively small size when compared to Type 2.

Case 1 This patient had a one year history of abdominal pain and diarrhoea before the barium study (Fig. 1). This demonstrated a narrowed area in the mid-descending colon with profuse polypoid tissue. The proximal bowel was distended. This lesion was at first thought to be a villous tumour, but at laparotomy the external appearance of the colon was in keeping with Crohn's disease. The appendix was also involved.

The opened bowel (Fig. 2) showed the extensive pseudopolyposis.

Case 2. Showed similar radiological appearances with complete obstruction to the passage of barium by a mass of small pseudopolyps (Fig. 3).

Case 3 also had a large collection of pseudopolyps though these were unassociated with any obstructive symptoms (Fig. 4). This case has not been included as an example of localized giant pseudopolyposis because of the more scattered nature of these pseudopolyps in the ascending colon.

Type 2: Localized giant pseudopolyposis

In these two cases, the pseudopolyps were much larger, measuring up to 2 cm diameter. Collections of these in a segment of colon gave rise to the appearance of a mass lesion within the colon.

Case 4 This patient presented with peri-anal abscesses and fistulae. Five years later he developed profuse diarrhoea and barium studies demonstrated Crohn's disease in both small and large bowel. A year later he had another enema demonstrating massive pseudopolyps in the sigmoid (Fig. 5) and colectomy was performed after this.

Case 5 showed similar appearances Fig. 6.

Type 3: Generalized pseudopolyposis

Here pseudopolyps of varying size are scattered diffusely throughout the colon from rectum to caecum.

Case 6 This patient had a long medical history starting with chronic active hepatitis in 1957. Ten years later she developed diarrhoea due to Crohn's disease. She had small bowel involvement and also a recto-vaginal fistula. Extensive pseudopolyposis was present throughout the bowel (Fig. 7).

Type 4: Long finger-like pseudopolyps

These curious structures presumably result from exuberant granulation tissue and may attain a considerable length. In one of the examples a pseudopolyp is 5 cm long while the others were 2–3 cm in length. It is of interest that they were found in the two patients with the longest history of disease.

Case 7 presented at another hospital with a five-year history of rectal bleeding, which was initially thought to be due to distal ulcerative colitis. Barium follow-through studies later showed changes of Crohn's disease in the ileum. Repeat barium studies two years later confirmed ileal involvement with fistula formation, and also showed long pseudopolyps at the hepatic flexure (Fig. 8).

Case 8 showed similar appearances in the sigmoid (Fig. 9).

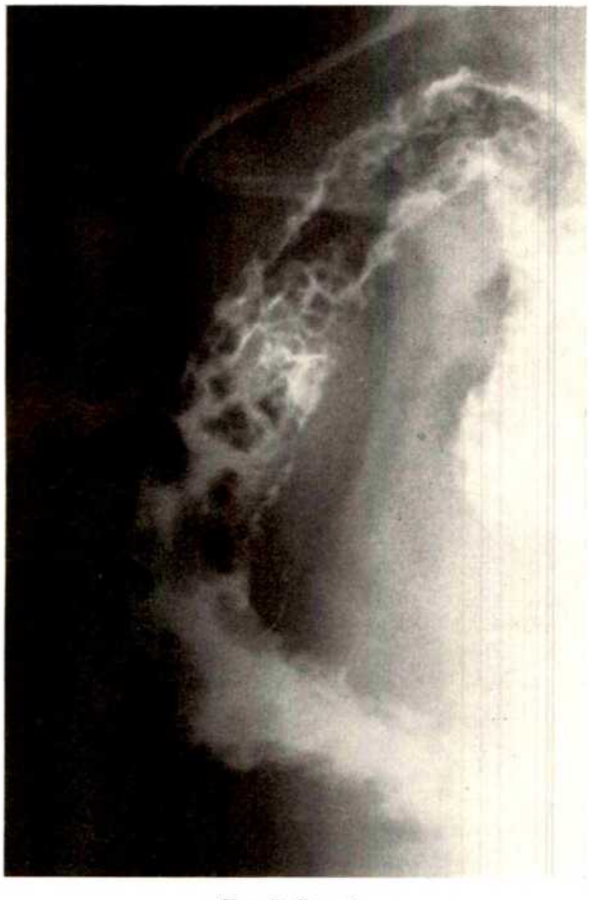


FIG. 7. *Case 6.*

Air-filled lateral view of the rectum during a barium enema. Pseudopolyps of varying size are shown and were present like this throughout the colon.

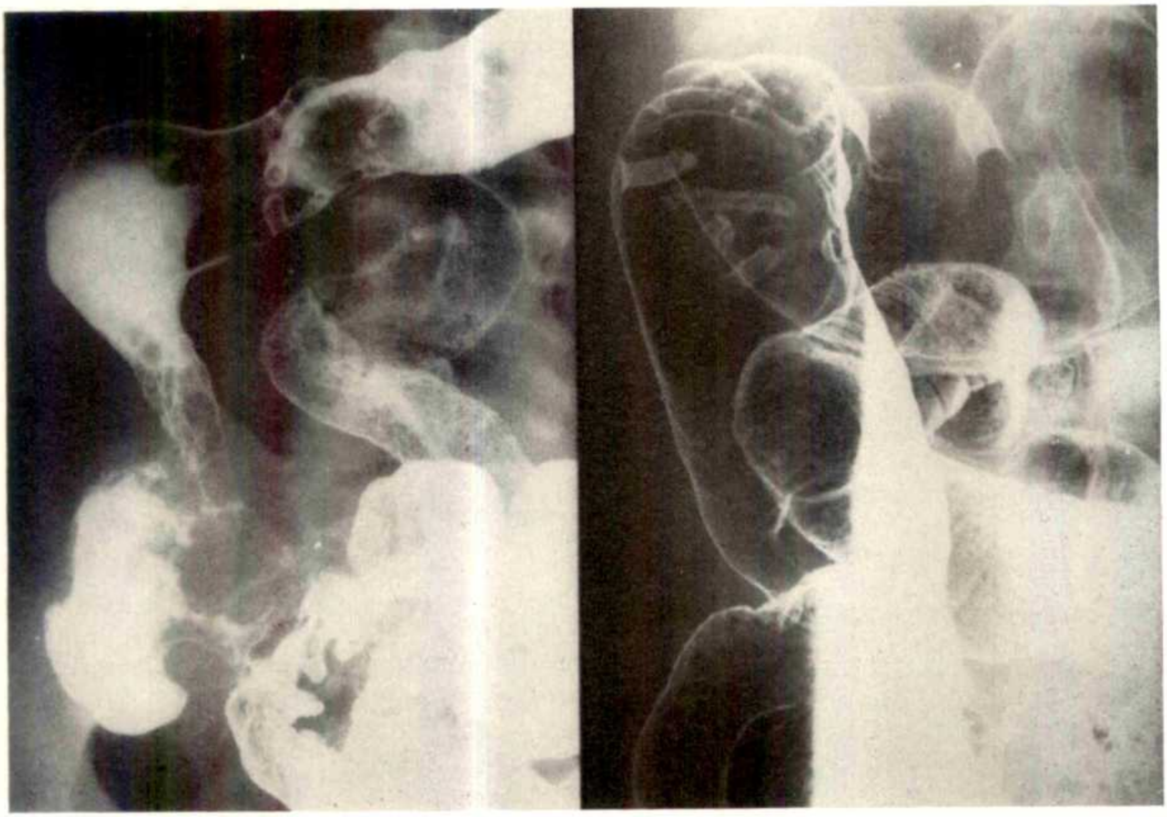


Fig. 8. *Case 7.*

Barium enema showing long finger-like pseudopolyps in the hepatic flexure. Also present are abnormalities in the terminal ileum and caecum secondary to Crohn's disease.

Discussion

Pseudopolyps in Crohn's disease are not an uncommon finding. According to Joffe (1977) they may represent either regenerating mucosal islands between areas of ulceration, oedematous polypoid tags or granulation tissue covered by epithelium.

They are of importance in two respects. Firstly, from the point of view of the differential diagnosis of colitis, the presence of pseudopolyps does not help in the distinction between Crohn's disease and ulcerative colitis. However, Crohn's colitis is suggested if they are situated proximal to a length of normal colon or if they are segmental in distribution. No distinction can be made on their actual shape or appearance.

Secondly, massive pseudopolyposis of the colon in Crohn's disease is of importance as a rare cause of obstructive symptoms. Unless there are clinical features, sigmoidoscopic findings or other radiological abnormalities to suggest Crohn's disease, the condition may be indistinguishable from a villous tumour except by colonscopy and biopsy, or at laporotomy.

Minor degrees of pseudopolyposis are not uncommon in Crohn's disease. These eight cases illustrate the grosser and more striking changes which may occur. The two examples of localized giant pseudopolyposis bring the total reported in the world literature to seven.

Summary

Eight cases of colonic pseudopolyposis due to Crohn's disease, illustrating the variety of appearances which may be found, are reported. Two of the cases showed what has been termed localized giant pseudopolyposis, which in two resulted in intestinal obstruction.

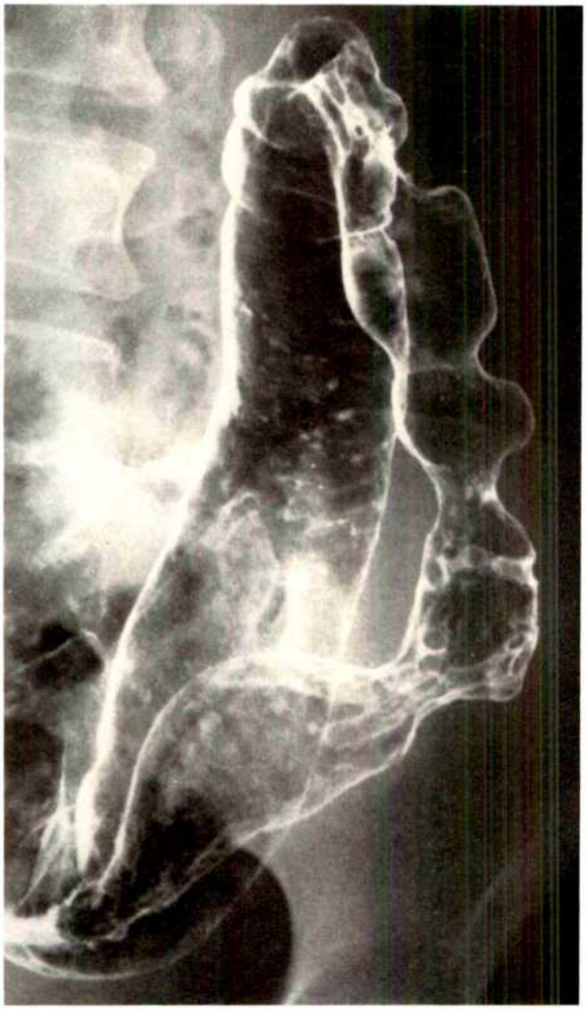


Fig. 9. *Case 8*.

Two very long pseudopolyps are demonstrated in the distal descending colon with a shorter one lying slightly more proximally.

REFERENCES

Ayre-Smith, G., 1977. Localized giant pseudopolyposis of the colon in granulomatous colitis. A case report and review of the literature. *British Journal of Radiology*, *50*, 916–917.

Berridge, F. R., 1975. Crohn's disease. A review of its diverse radiological appearances. *Journal of the Irish Colleges of Physicians and Surgeons*, *5*, 59–66.

Ferrucci, J. T., 1972. Case records of the Massachusetts General Hospital. *New England Journal of Medicine*, *286*, 147–153.

Hinrichs, H. R., and Goldman, H., 1968. Localized giant pseudopolyps of the colon. *Journal of the American Medical Association*, *205*, 248–249.

Joffe, N., 1977. Localised giant pseudopolyposis secondary to ulcerative or granulomatous colitis. *Clinical Radiology*, *28*, 609–616.

Laufer, I., 1977. Air contrast studies of the colon in inflammatory bowel disease. *Critical Reviews in Diagnostic Imaging*, *9*, 421–447.

Margulis, A. R., Goldberg, H. I., Lawson, T. L., Montgomery, C. K., Rambo, O. N., Noonan, C. D., and Amberg, J. R., 1971. The overlapping spectrum of ulcerative and granulomatous colitis. A roentgenographic-pathologic study. *American Journal of Radiology*, *113*, 325–334.

Marshak, R. H., 1975. Granulomatous disease of the intestinal tract (Crohn's disease). *Radiology*, *114*, 3–22.

Schneider, R., Dickersin, G. R., and Patterson, J. F., 1973. Localised giant pseudopolyposis. A complication of granulomatous colitis. *American Journal of Digestive Diseases*, *18*, 265–270.

Stanley, P., Kelsey-Fry, I., Dawson, A. M., and Dyer, N., 1971. Radiological signs of ulcerative colitis and Crohn's disease of the colon. *Clinical Radiology*, *22*, 434–442.

Welin, S. and Welin, G., 1976. Crohn's disease and ulcerative colitis. In *The Double Contrast Examination of the Colon Experiences with the Welin Modification*, pp. 65–95 (Georg Thieme, Stuttgart).

Wills, J. S., and Han, S. S., 1977. Localised giant pseudopolyposis complicating granulomatous ileocolitis. *Radiology*, *122*, 320.

Wolf, B. S., and Marshak, R. H., 1962. Granulomatous colitis (Crohn's disease of the colon). *American Journal of Roentgenology*, *88*, 662–670.

Young, A. C., 1969. Radiology of the large bowel. In *A Text Book of X-Ray Diagnosis by British Authors*, (eds.) S. Cochrane Shanks and P. Kerley, vol. 4, pp. 387–484 H. K. Lewis and Co., London).

Book review

Cardiac Catheterization and Angiocardiography. By D. Verel, R. G. Grainger and D. R. Naik, pp. xv + 239, illust., 3rd edition 1978. (Churchill Livingstone, Edinburgh) £13·00.

This book was first published in 1969. It immediately became an invaluable primer for any trainee cardiologist or radiologist with an interest in angiocardiography. Rapid advances in this field have necessitated much re-writing for this third edition. The increasing use of ultrasound has been responsible for an excellent new section on echocardiography by Dr. Naik, while the increased demand for coronary arteriography is mirrored in a considerably extended chapter on that procedure.

The sections on calculated data and radiographic equipment have also been largely re-written.

The text is thus thoroughly up-to-date and is in turn backed by an increased number of useful references. The lucid and succinct style of earlier editions is retained, while the whole book extends to little more than 200 pages. It is easy and enjoyable reading which should be mandatory for any senior registrar in radiology with an interest in this complicated field. I doubt that he or she will find better advice in much bigger books.

The atlas at the end of the book is excellent. If I could make one plea it would be for a greater number and selection of coronary arteriograms.

C. D. R. Flower.

1978, *British Journal of Radiology*, *51*, 788–792

Hepatic oil embolism following lymphography*

By H. Ngan, M.B., M.R.C.P., F.R.C.R.†

Queen Mary's Hospital, Roehampton, London, S.W.15

and K. W. James, M.A., M.B., F.R.C.R.

Velindre Hospital, Whitchurch, Cardiff

(*Received August, 1976 and in revised form April, 1978*)

ABSTRACT

Lymphograms of 1,000 patients were reviewed with special reference to the occurrence of hepatic oil embolism following the procedure. Oily contrast medium ("Lipiodol" ultra-fluid) was found in the liver in seven cases, five of whom had carcinoma of the cervix uteri. Hepatic oil embolism was not encountered in patients with lymphomas in this series. Complete or partial lymphatic obstruction was present in all seven cases and one patient had almost complete obstruction of the inferior vena cava. Malignant disease need not always be the predisposing factor since hepatic oil embolism occurred in one patient with retro-peritoneal fibrosis. The routes through which the contrast medium may reach the liver are discussed and lymphatico-portal communications in the mesentery are thought to play an important role. Contrast was invariably seen in the liver within two hours of commencement of the injection and was still faintly visible in one case three and a half months later. The way in which the contrast-pattern in the liver changes with time is described. An attempt is made to correlate the radiological appearances with the fate of the contrast medium in the liver.

Opacification of the liver following lymphography was first described by Leger *et al.* (1961). Two radiological patterns are recognized: one of linear densities, usually called "arborizing" and one of uniformly distributed punctate opacities, often described as "granular". The phenomenon is rare. Chavez *et al.* (1968) organized a world-wide survey of 17,000 lymphograms and found 36 cases of hepatic oil embolism, an incidence of 0.19%. Thornbury (1970), however, found two cases in 250 lymphograms, an incidence of 0.8%. The present series of 1,000 lymphograms from The General Hospital, Nottingham, The Westminster Hospital, London and Velindre Hospital, Cardiff, revealed seven cases, an incidence of 0.7%.

Table I shows the incidence of hepatic oil embolus in this series. One case occurred in a patient with oat-cell carcinoma of the bronchus and another in a patient with retro-peritoneal fibrosis while five cases were associated with squamous-cell carcinoma of the cervix uteri. This corresponds with the finding of Chavez *et al.* (1968) that hepatic oil embolism is very rare in lymphomas. In his series, 18 of the 36 cases were associated with testicular cancers and a further nine were associated with carcinomas of the cervix. Thus, although hepatic oil embolism does occur in

TABLE I

THE INCIDENCE OF HEPATIC OIL EMBOLISM

Pathology	Number of cases of hepatic oil embolism	Total number of cases
Lymphomas	0	440
Testicular tumours	0	148
Melanomas	0	113
Gynaecological cancer	5 all cervical cancers	94
Lymphoedema	0	40
Miscellaneous	2 1 oat-cell carcinoma 1 retro-peritoneal fibrosis	165
All cases	7 An incidence of 0.7%	1000

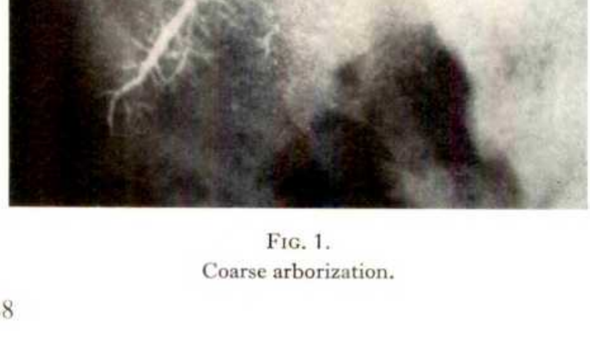


FIG. 1.

Coarse arborization.

---

*Paper read at Congressus Tertius, Societatis Radiologicae Europaeae, Edinburgh, June 1975 by Dr. D. K. L. Davies of Velindre Hospital.

†Now at Queen Mary Hospital, Hong Kong.

non-malignant diseases like filariasis and retroperitoneal fibrosis, the majority of cases are associated with carcinomas metastatic to the retroperitoneal lymph nodes.

Radiological Findings

Two basic appearances were found, the arborizing and the granular. Both these may be subdivided into coarse and fine types, giving four possible radiological patterns.

Coarse arborization is not the common radiological appearance of hepatic oil embolism but was demonstrated in one of our cases (Fig. 1) and is also illustrated in the paper by Perez-Tomayo *et al.* (1963). Comparatively large vascular-looking structures 0.5 cm to 3.0 cm in length and 1 mm to 2 mm in diameter, with a main trunk giving rise to finer branches, are opacified. This finding is identtical with that produced in dogs by Chavez *et al* (1965) where contrast material was injected directly into the mesocolonic vein, a tributary of the portal vein. Fine arborization is the most commonly recognized pattern of hepatic oil embolism in man (Fig. 2). The linear opacifications, measuring only a maximum of 1.5 cm in length and 1 mm in diameter, are much smaller but more numerous, with fewer "branches" arising from each "stem".

Myriad irregular-shaped blobs of contrast 1 to 2 mm in diameter are distributed more or less uniformly throughout the liver in the coarse granular pattern (Fig. 3). In the fine granular pattern the opacities are 0.5 mm or less in diameter and produce a dense and almost homogeneous stippling. Superimposed on both types of granular pattern and clearly seen on our original films, is a criss-cross pattern of arborizing black lines. Attention does not appear to have been directed to these previously but they are well-reproduced in an illustration in an article by Bodie and Linton (1971).

There is a definite evolution of the patterns with time. This is shown in Table II which groups them according to the time after injection that the films were taken. The hepatic areas on all the available films of our seven patients were scrutinized. Sixteen radiographs showed only one pattern of the four possible types. Two showed two patterns on the same film and one radiograph showed three patterns. Coarse arborization was seen only once, when it appeared together with fine arborization and coarse granularity, one hour after commencement of the injection. It is seen from Table II that the arborizing appearance prevails during the early hours after injection whereas, a day or so later, the coarse granular pattern is the predominant finding. A week

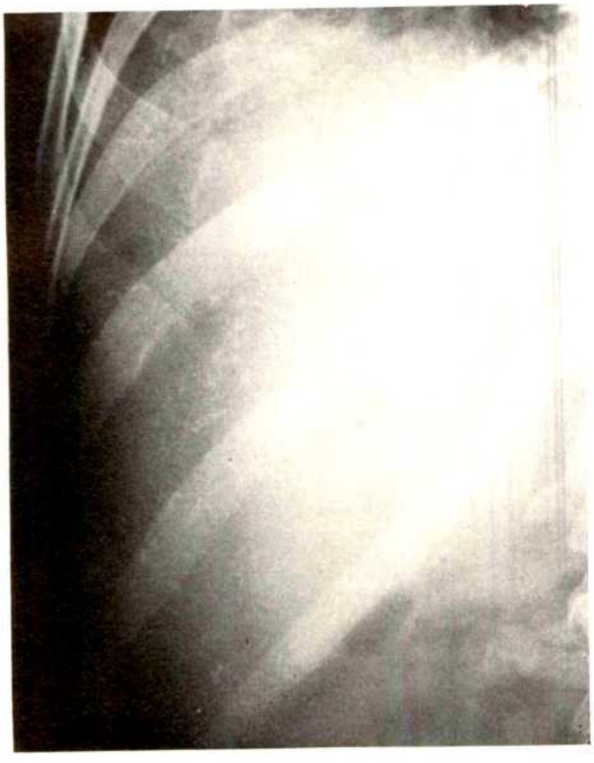


Fig. 2.
Fine arborization.

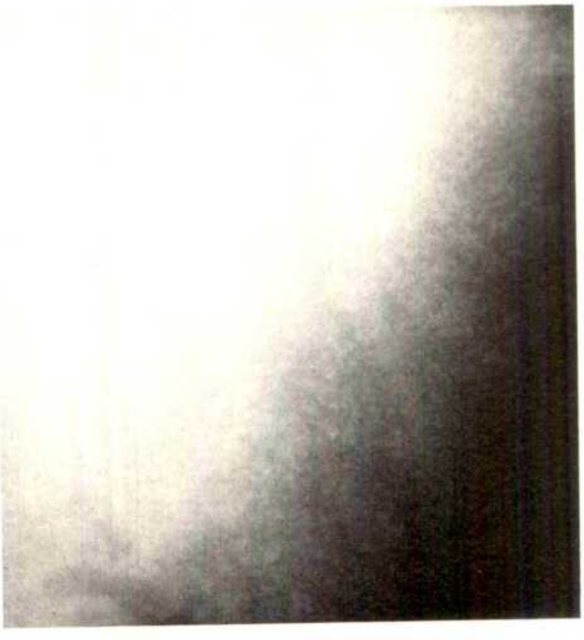
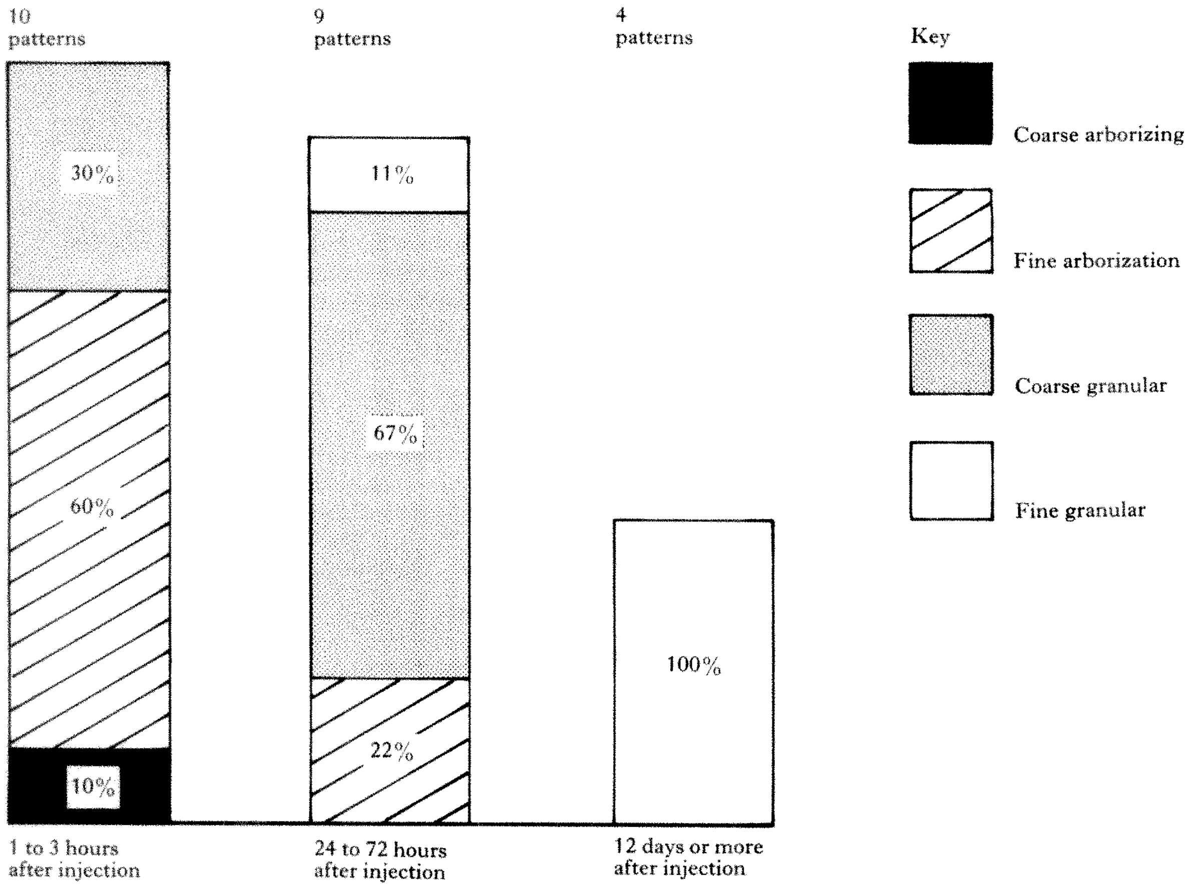


Fig. 3.
Coarse granular pattern.

TABLE II

THE CHANGE OF RADIOLOGICAL PATTERNS OF HEPATIC OIL EMBOLISM WITH TIME



or so later only the fine type of granular appearance is seen. Previous reports of the contrast having been cleared from the liver by the third to seventh day after injection (Markovits *et al.*, 1965) may have been due to failure to recognize the faint, almost homogeneous pattern of fine granular opacification.

The seven cases showing liver opacification are summarized in Table III. It will be seen that all of them showed some degree of bilateral lymphatic obstruction which was complete in four and occurred at the level of the fifth lumbar or first sacral vertebrae. One case showed complete unilateral obstruction. Evidence of retrograde flow was seen in three cases. Venography was performed in one case and showed obstruction to the inferior vena cava.

DISCUSSION

Leger *et al.* (1961) identified the linear arborizations of hepatic oil embolism as contrast present in hepatic lymphatics and they suggested that there were collateral anastomoses between the pelvic lymphatics and those of the liver which allowed contrast to flow directly from the former into the latter when lymphatic obstruction was present. However, none of our cases or those in the literature has demonstrated such a connection. Moreover, the size of the structures outlined in coarse arborization strongly suggests that the shadows are blood vessels and the reproduction of the phenomenon in dogs by Chavez *et al.* (1965) by the injection of oily contrast into the mesocolonic vein affirms that the contrast reaches the liver by way of the portal vein. A case of Chavez *et al.* (1965), a further one of Perez-Tomayo *et al.* (1963) and our first case (Fig. 4) all demonstrated venous-like opacifications in the pelvis, thus there is little doubt that peripheral lymphatico-venous communications exist.

For some time it was thought that concurrent systemic venous obstruction was necessary, in addition to lymphatic obstruction, for hepatic oil

TABLE III

DETAILS OF THE CASES

Diagnosis	Time of hepatic opacification	Lymphatic obstruction	Comment
1. Carcinoma of cervix	2 hours	Complete and bilateral at 5th lumbar vertebra	Opacification of inferior mesenteric vein
2. Carcinoma of cervix	1 hour	Complete and bilateral at 5th lumbar vertebra	Contrast in left renal pelvis
3. Carcinoma of cervix	2 hours	Complete and bilateral at 5th lumbar vertebra	
4. Carcinoma of cervix	1 hour	Complete and bilateral at sacroiliac joints	
5. Carcinoma of cervix	2 hours	Complete at right sacroiliac joint. Partial in upper para-aortic nodes	Retrograde filling of mesenteric lymph nodes (superior mesenteric)
6. Carcinoma of the bronchus, (oat-cell)	2 hours	Presumed to be partial and in the upper thoracic duct (cisterna opacified for 12days)	
7. Retro-peritoneal fibrosis	1 hour	Partial, on the right at 5th lumbar vertebra, on the left at the para-aortic region	Almost complete obstruction of the inferior vena cava at 3rd lumbar vertebra. Numerous lymphatic collaterals

embolism to take place. The route suggested was from the engorged pelvic lymphatics to the systemic veins via lymphatico-venous communications and from the systemic veins to the tributaries of the portal vein, which would act as a collateral when the inferior vena cava or its branches was obstructed. Hecht *et al.* (1968) demonstrated, however, that hepatic oil embolism could occur in the presence of a completely patent inferior vena cava. Figure 4 suggests that there are direct links between the lower lumbar and pelvic lymphatics and the inferior mesenteric vein and hence the portal vein.

The constant finding of severe lymphatic obstruction and, in some cases radiological demonstration of retrograde flow of lymph, supports a hypothesis that requires retrograde flow of contrast from the retro-peritoneal area into the mesentery where it gains entry to the portal system via lymphatico-venous communications.

Having agreed that the arborizing patterns probably represent opacification of the branches, first the large, then the smaller, of the portal vein, where is the contrast when it produces the granular patterns? One might think that the contrast is taken up by the Kuppfer cells of the reticulo-endothelial system. However, Chavez *et al.* (1965) showed in their dogs that an *emulsion* of the contrast oil did not give

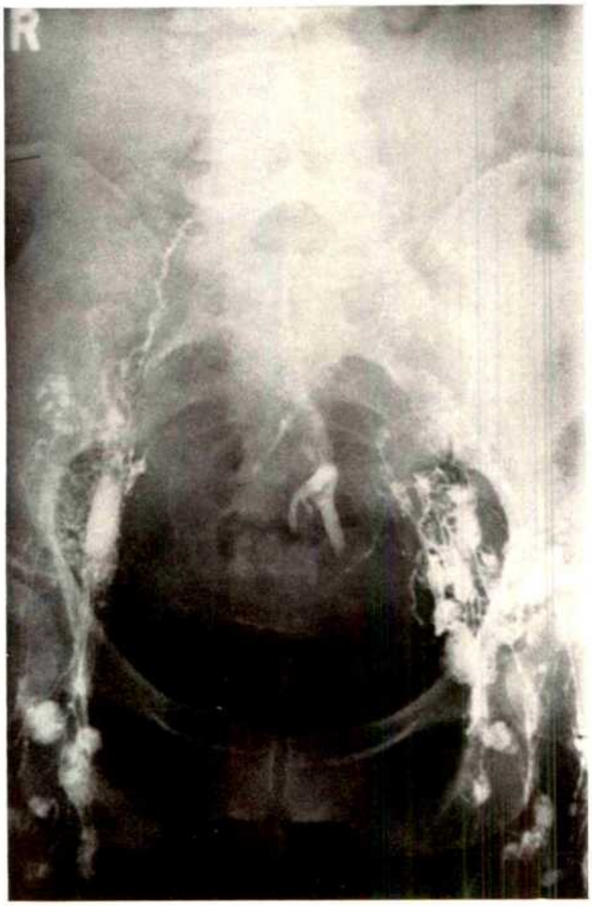


FIG. 4.

Opacification of a branch of the inferior mesenteric vein.

opacification of the liver after injection into the portal system.

In dogs that had suffered hepatic oil embolism 8 to 12 days previously, histology of the liver showed multiple fat droplet thromboses of the finest branches of the portal vein with many of these thrombi already showing recanalization and organization with giant cell infiltration. It seems likely that the contrast fragments eventually rest in the sinusoids. The black arborizing lines seen in the granular patterns may represent tubular structures, perhaps bile ducts or fine branches of the vascular network, but could equally well be summation artefacts due to the superimposition of layer upon layer of liver tissue, each one bearing a fairly regular radiological pattern of contrast (Carstairs, 1961). Eventually, lipolysis of the oily medium by the hepatic cells allows the vessels to completely recanalize. In dogs, Chavez *et al.* (1965) found that liver biopsy five months after hepatic oil embolism, when the contrast had disappeared radiologically, was essentially normal.

Conclusion

We have attempted to define the circumstances in which hepatic oil embolism following lymphography occurs. Substantial, usually bilateral, lymphatic obstruction is necessary for its production. The phenomenon thus is most common in patients with advanced cancers metastatic to retro-peritoneal nodes. We suggest that direct access of the contrast to the portal system can take place through lymphatico-portal communications after retrograde flow in mesenteric lymphatics. The evolution of the radiological appearances has been described.

REFERENCES

Bodie, J. F., and Linton, D. S., 1971. Hepatic oil embolisation as a complication of lymphangiography. *Radiology, 99*. 317–318.

Carstairs, L. S., 1961. The interpretation of shadows in a restricted area of a lung field on the chest radiograph. *Proceedings of the Royal Society of Medicine, 54*, 978–980.

Chavez, C. M., Berrong, L. G., and Evers, C. G., 1965. Hepatic oil embolism after lymphangiography. *American Journal of Surgery, 110*, 456–460.

Chavez, C. M., Picard, J. D., and Davis, D., 1968. Hepatic oil embolisation following lymphography. In *Second International Congress of Lymphography*, Miami Beach, Florida, March 15th to 20th.

Hecht, H., Berdon, W., and Baker, D., 1968. Hepatic oil embolisation following lymphangiography in a child with neuroblastoma. *American Journal of Roentgenology, 104*, 860–864.

Leger, L., Buchet, R., Bitry-Boely, C., and Premont, M., 1961. Introduction de l'étude de la lymphographie hepatique. *La Presse Médicale, 69*, 1981–1982.

Markovits, P., Grellet, J., and Blache, R., 1965. A propos des hepatographies observées au cours des lymphographies. *Annals de la Radiologie, 8*, 535–546.

Perez-Tomayo, R., Thornbury, J. R., and Atkinson, R. J., 1963. "Secondlook" lymphography. *American Journal of Roentgenology, 90*, 1078–1086.

Thornbury, J. R., 1970. In *Progress in Lymphology 2*, Edited by M. Viamonte, P. R. Koehler, M. Witte and C. Witte. pp. 105–109, (Georg Thieme Verlag, Stuttgart).

Book review

Radiation exposure from consumer products and miscellaneous sources. NCRP Report No. 56, pp. iv+80, illus., 1977 $4.00.

In this technological age man may be exposed to radiation from many sources, quite apart from those frequently discussed: medical procedures, fall-out from weapons tests and nuclear power. The other sources include some familier ones, *e.g.* television receivers or luminous watches, but also the less known radioactivity in spectacles, dentures, tobacco and fuel for cooking, and X rays from electron microscopes. The need for security has added exposure from airport inspection, personnel scanning and identification cards. Recycled "Radon seeds" contaminate the gold in wedding rings.

All these sources, and the doses resulting from them, are reviewed in this NCRP Report. Although the data refer specifically to the United States, their significance is world wide. It is not quite clear why some sources were included and others excluded from the survey. Thus, radioactivity in walls of buildings, or road surfaces—usually treated as part of the natural background—is included, but the increased cosmic ray dose when flying in jet airplanes is left out, although the dose to passengers from radioactive materials carried in them is discussed.

The largest whole-body dose is indeed from the natural radioactivity of building materials—3 to 5 mrem for the U.S. population. Up to 0·5 mrem results from luminous clocks and watches. Not included in this are digital watches with LCD display activated by tritium; such a watch may contain 200 mCi of tritium which leaks slowly.

Much larger doses are delivered by some sources to limited parts of the body. Smoking results in an annual dose of 8 rem to the bronchial epithelium. Cancer of the lung is of course a much greater hazard of smoking, but there may be a synergistic effect. Lenses in some spectacles contain enough radioactivity to give an annual dose of 1–4 rem to the cornea. The largest doses result from dental protheses to which uranium salts were added to give a natural colour to the denture; the dose to superficial layers of tissue in contact with the teeth is 60 rem annually. Such is the price of vanity.

J. Rotblat.

1978, *British Journal of Radiology*, *51*, 793–798

Volume changes in the rat renal cortex during urography

By V. Hegedüs, M.D., Ph.D., P. Faarup, M.D., Ph.D., T. Nørgaard, M.D. and C. Lønholdt, M.D.

From the Department of Experimental Radiology, University Hospital Glostrup and Renal Laboratory, University Institute of Pathology, Copenhagen, Denmark.

(*Received January, 1978 and in revised form March, 1978*)

ABSTRACT

At different periods of urography rat kidneys were instantly frozen at −165°C. Using appropriate histological techniques and planimetry of different cortical compartments and fractions the structural background of renal cortical volume variations during urography was elucidated. The renal cortex reacted to intravenous injection of hypertonic contrast medium with an immediate increase of volume, followed by a decrease from 30 to 60 seconds. Measuring the volume shares of different cortical compartments, the complex nature of cortical volume variations during the first minutes of urography could be demonstrated. Subdivision of the tubular compartments into cellular and luminal fractions showed even greater complexity of volume variations. All the major cortical volume changes came to an end approximately three minutes after the injection.

Variations in kidney size during urography—with and without different wash-out techniques—have been used for diagnostic purposes (Dorph and Øjgaard, 1973a; 1973b; 1975). Furthermore renal haemodynamics during urography have been correlated with variations of kidney size (Dorph *et al.*, 1977). Renal lymphatic concentrations of the contrast medium, and the relationship between renal lymph flow and kidney size variations during urography have also been investigated (Hegedüs *et al.*, 1974; Cramer and Hegedüs, 1977), suggesting participation of the renal interstitium in the variations of renal size during urography.

However, the structural background to the volume changes of the kidney has not been investigated previously, since conventional histological techniques are inappropriate for this purpose (Faarup *et al.*, 1971). Post mortem changes and tissue fixation obscure any information about minute volume changes of the different renal compartments found in the functioning kidney (Hegedüs and Faarup, 1972).

In this investigation a histological technique was used which maintains the *in-vivo* structure of the nephron during its actual functional state. Thus it was possible to evaluate the volume changes of the different compartments within the renal cortex which make up the macroscopic volume changes of the kidney during urography. With this technique, no information about the volume variations of the non-cortical parts of the renal parenchyma was gained.

MATERIAL AND METHODS

Twenty-eight male rats (weight 250 g) were used. The animals were anaesthetized with intraperitoneal sodium pentobarbital, and this was followed by careful operative exposure of the left kidney. An intravenous bolus of sodium iothalamate (400 mg I/kg/body weight) was then injected into the left jugular vein. After the injection, at 30 sec, 1, 2, 3, 6, and 15 minutes the exposed left kidney was rapidly removed from a series of animals and frozen in isopentane at −165°C. Four micron thick cryostat sections were cut in tangential sections taken identically in each animal from the poles and the lateral edges of the kidneys. The sections were freeze-dried in a desiccator, placed close to osmic acid crystals. In this way the histological sections were stained by the osmic acid vapour during dehydration. Finally the freeze-dried sections were mounted in paraffin oil, and according to the technique described by Faarup *et al.* (1971), the different tubules of the nephrons were easily distinguished microscopically.

By counting the number of tubules in identical cortical areas from each kidney in the freeze-dried sections the percentage volume change of the total renal cortex was estimated. Furthermore, volume changes of the following cortical compartments were investigated:

(1) Proximal tubules (lumen and cellular volume)
(2) Distal tubules (lumen and cellular volume)
(3) Interstitial tissue including the peritubular capillaries.

The quantitative estimation of the volume changes of the different tubular and interstitial compartments was done by planimetry of drawings, which were made by standardized projection of the slides. For each period of observation four animals were used, and in each kidney nine sections containing at least 400 tubules were studied by this method. The data obtained were statistically analyzed, using Wilcoxons rank test. The right kidneys of the rat were conventionally fixed in buffered formaline and

---

Supported by a grant from "Danish Hospital Foundation for Medical Research, Region of Copenhagen, Faroe Islands and Greenland".

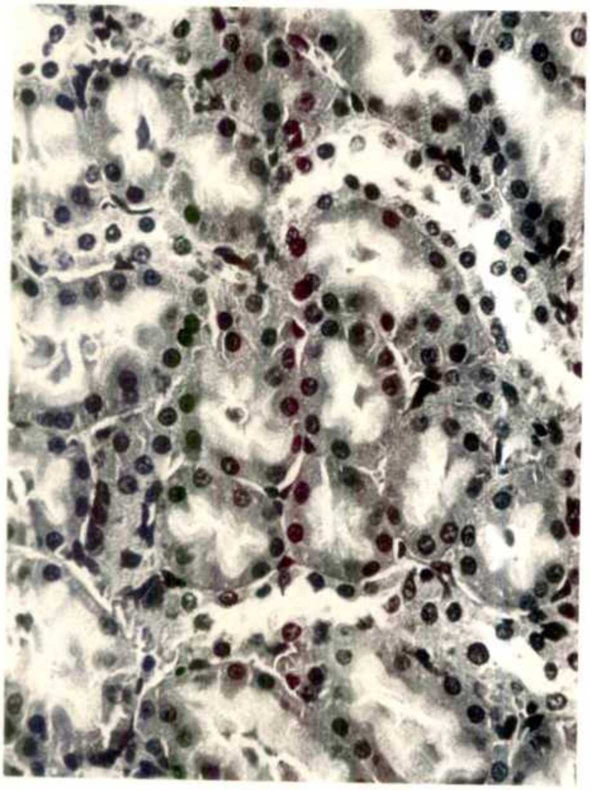


FIG. 1.

Conventionally prepared, formalin fixed section from the renal cortex in which the lumina of the tubules are occluded. The interstitium containing the peritubular capillaries is collapsed. (H & E, ×440).

were investigated by conventional histological procedures. In this way it was possible to ensure that the animals were not suffering from renal disease.

RESULTS

(1) *The histological structure of the conventionally fixed right kidneys during urography.*

All kidneys were of similar histological appearance, regardless of the interval between the injection of the contrast medium and fixation (Fig. 1). The proximal tubules were found occluded, and the interstitial space including the peritubular capillaries was collapsed.

(2) *The histological structure of the instantly frozen left kidneys during urography.*

Definite histological changes in the instantly frozen cortex from the left kidneys during the phases of urography could be observed (Fig. 2).

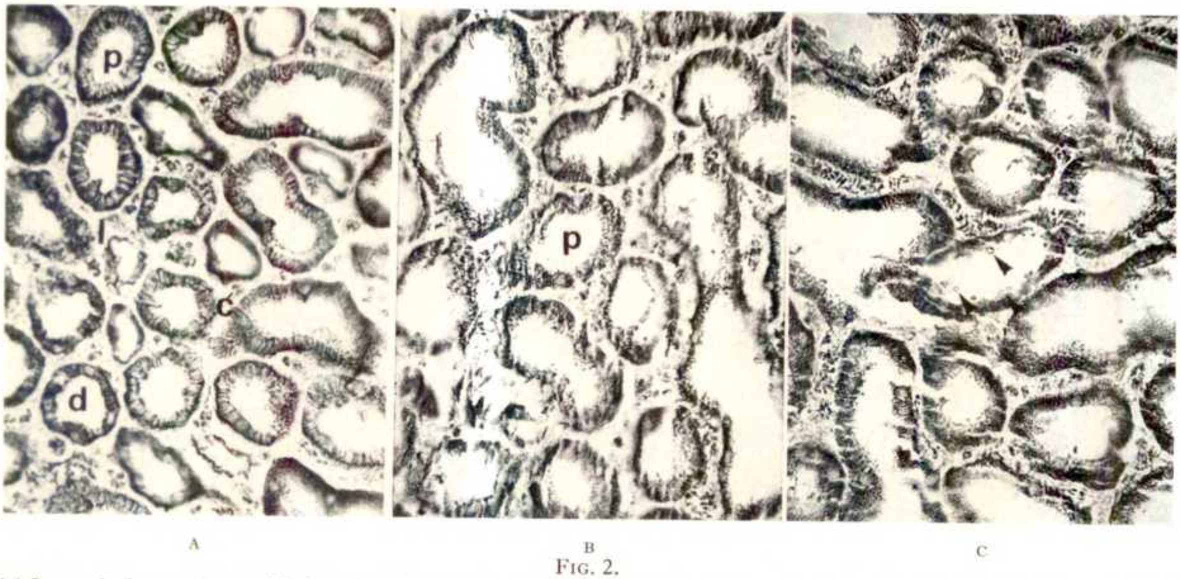


FIG. 2.

(A) Instantly frozen, freeze-dried section from the renal cortex stained by osmic vapour in which the *in vivo* morphology of the tubules is well preserved, including the patent tubular lumen (p proximal-, d distal tubules). The interstitial tissue (i) is not collapsed and the intertubular capillaries (c) are easily identified, the lumen being patent.

(B) Freeze-dried section from the renal cortex, 30 seconds after the injection. The lumina of the proximal tubules (p) are dilated and the cells are diminished in size. The capillary walls are badly recognized in the interstitium. Probably due to the osmotic effect of the contrast medium, the technical quality of the section is inferior to Fig. 2a.

(C) Freeze-dried section from the renal cortex two minutes after injection of the contrast medium. In the lumen of the distal tubules the contrast medium can be recognized in small globules (arrows) formed due to the freeze-drying of the highly concentrated contrast medium in the tubular fluid.

In control rat kidneys (without contrast medium) histological differentiation of the interstitial connective tissue from the peritubular capillaries was easy in the freeze-dried, osmium-stained cryostat sections, as described previously (Faarup *et al.*, 1971) (Fig. 2A). In the animals injected with contrast medium this differentiation could not be made with the same degree of confidence, because of a lesser degree of osmophilia in the interstitial tissue of the kidneys (Fig. 2B). Therefore the peritubular capillaries were included in the interstitial volume for the quantitative estimation of volume changes. In the lumen of the distal tubules drops of contrast medium were recognized from 30 sec up to 3 min after the i.v. injection (Fig. 2C). The same type of drops were seen also in the collecting tubules appearing 1 min after the injection. Similar findings were never observed in the proximal tubules.

(3) *Estimation of cortical volume changes in the functioning kidney during urography.*

In the instantly freeze-dried kidneys taken at various intervals after the injection of contrast medium, the proximal and distal tubules and the intertubular insterstitial space could easily be distinguished microscopically (Fig. 2). Employing the method described the total cortical volume changes could be estimated during different phases of urography. The mean changes depicted in Fig. 3 consist of rapid increase of cortical volume followed by a decrease, and two minutes after the injection again a slow increase to a few percent above the pre-urographic volume ($p < 0.01$).

(4) *Relative volume changes of the cortical compartments during urography.*

Using planimetry it was possible to estimate *relative* volume variations of the different cortical compartments. This means that the volumes obtained at each phase of urography represent only mutual percentage differences between the compartments and not absolute volumes. All of these variations are shown in Fig. 4.

(a) *Relative volume variations of the interstitium.* In the control kidneys the share of the interstitium as related to the total cortical volume was approximately 30%. This share was already decreased 30 sec after the i.v. injection and reached its minimum at three minutes with a relative volume of 24%. Even 15 min after injection the interstitium had a reduced volume as compared with the pre-urographic state. The most significant changes ($p < 0.01$) are between nought and three minutes, while the significance of the difference between the initial and final volumes is questionable.

(b) *Relative volume variations of the proximal tubules.* The 62% share of proximal tubules in the control kidneys decreased one minute after injection to 58% of the cortical volume ($0.01 < p < 0.05$), to be followed by a rapid increase to 67% at two min after the injection ($p < 0.01$). After the second minute and through all phases of observation the share of the proximal tubular volume slowly decreased and at 15 minutes was not significantly different from the initial volume (Fig. 4).

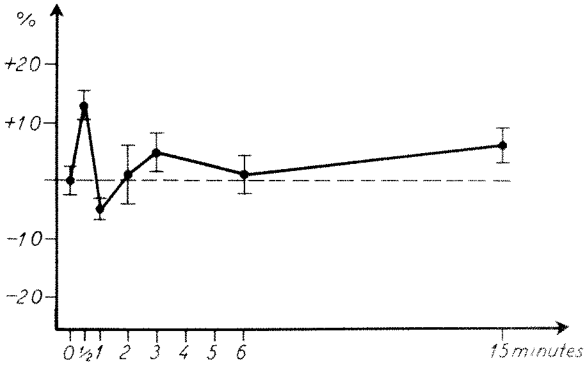


FIG. 3.

Volume variations of the renal cortex during urography. Already 30 seconds after the i.v. injection of the contrast medium a marked increase of the cortical volume was shown. Standard deviations are indicated.

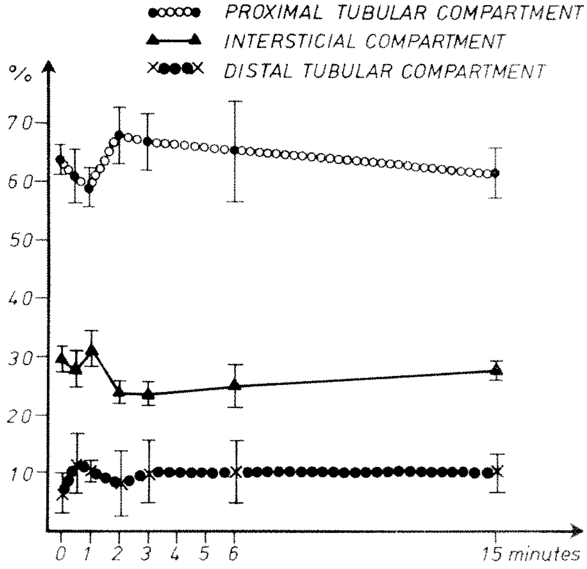


FIG. 4.

Volume shares of the different cortical compartments during urography. At each period of measurement the sum of the three compartments equals 100%. Standard deviations are indicated.

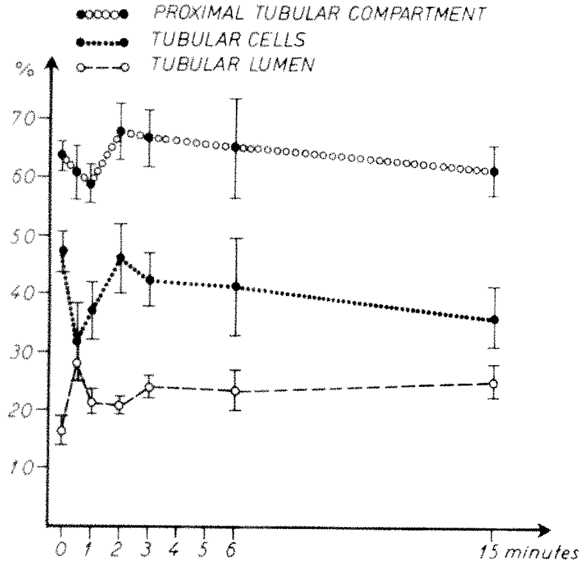


FIG. 5.

Volume variations of the cellular, and luminal fractions within the proximal tubular compartment. Standard deviations are indicated.

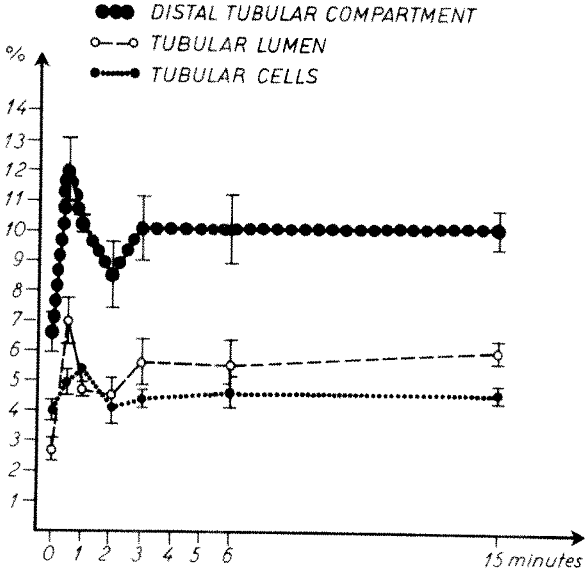


FIG. 6.

Volume variations of the cellular and luminal fractions within the distal tubular compartment. The scale of % is enlarged fivefold as compared to Figs. 4 and 5. Standard deviations are indicated.

However, observing the variations within the proximal tubular compartment (lumen versus tubular cells), the relations are entirely different. As shown in Fig. 5 the variations between these fractions at each period of urography were inversely related, as is easily recognizable during the first three minutes of the experiment ($p < 0.01$). The most important finding here is that despite the rapid decrease of the relative volume of the proximal tubules during the first minute the proximal tubular lumen is dilated from the very beginning of urography, indicating immediately increased primary urinary flow after injection of contrast medium. It is also shown that despite the increased tubular lumen during the first minutes of observation, the decreased cellular volume may be responsible for the decreased share of the proximal tubular volume.

(c) *Relative volume variations of the distal tubules.* In the control kidneys the distal tubular compartment was only 6.5% of the total cortical volume. Figure 6 shows that the share of this fraction doubled during the first 30 seconds after the i.v. injection, followed by a decrease with a minimum at two minutes, and then a rise ($0.01 < p < 0.05$). From the third minute and through the entire period of observation the share of the distal tubules remained approximately 3.5% above the control levels ($0.01 < p < 0.05$). It is also interesting to observe that, contrary to the proximal tubular compartment, the volume variations in the two distal tubular fractions—tubular lumen and tubular cells—followed each other ($p < 0.01$). These parallel changes may reflect increased urinary flow through the distal tubules and relative inactivity of the distal tubular cell as far as reabsorption and excretion are concerned.

DISCUSSION

It was previously shown both in man and animals that the kidney reacts to i.v. injection of hypertonic contrast media with considerable volume variations during the first minutes of investigation (Swann, 1960; Dorph and Øjgaard 1973a; 1973b; 1975; Cramer and Hegedüs, 1977; Dorph *et al.*, 1977).

Measuring variations of kidney size, renal haemodynamic and renal lymphatic flow during the urographic procedure, no significant differences were seen between the conventionally used contrast media (Hegedüs *et al.*, 1974; Cramer and Hegedüs, 1977; Dorph *et al.*, 1977). All changes observed could be related solely to the osmotic effect of the contrast media (Bördalen *et al.*, 1970). Therefore in this investigation only one of the hypertonic contrast media was used. In the present experimental investigation the contrast medium was given in doses comparable to those used in man during urography.

The purpose of this presentation was to elucidate the complex nature of cortical volume variations, which may have a considerable bearing on renal size variations during urography, since more than the half of the kidney is made up of cortex (Hegedüs and Faarup, 1972). Although measurements of areas of cortical compartments and fractions at certain periods of urography were performed, they may be accepted as reflections of volumetric changes.

We were interested in the following questions: (a) Which type of measurable changes in the different renal compartments contribute to the total renal volume variations which we can observe at urography? (b) Which of these can be related to the renal cortex? (c) During which period of urography are these variations significant for diagnostic purposes in the diseased renal cortex?

To this end small animals were used as only in these small kidneys could instant *in-vivo* fixation be achieved. However, owing to the small size of the kidneys investigated the changes in the total kidney volume could not be evaluated directly with confidence. Although kidneys of dogs and rats are not directly comparable it is striking to see that by comparison with the approximately 5% enlargement of total renal size seen in big animals (Cramer and Hegedüs, 1977; Dorph *et al.*, 1977), the cortical volume in rats increased by 13% during the initial period of urography. Extremely complex volume variations within the cortical compartments and fractions could be seen during the first minutes of urography (Figs. 4, 5 and 6). Although the complexity of these changes inhibited direct measurement of the volume shares of the different cortical compartments and fractions, they could be estimated in relative amounts, *i.e.* we expressed their mutual volume variations with regard to the actual size of the cortical volume. In this way we found interesting characteristics of volume variations within the renal cortex, probably producing the major part of volume changes of the whole kidney at the very beginning of urography.

It was surprising to observe that despite verified interstitial changes comprising increased subcapsular pressure, interstitial pressure and lymphatic flow during urography (Gootschalk and Mylle, 1957; Swann, 1960; Lindgren and Saltzman, 1974; Cramer and Hegedüs, 1977), the present investigation indicates that the contribution of the cortical interstitium to the volume changes is quantitatively of minor importance (Fig. 4).

During the first 30 seconds the total cortical volume increases by approximately 13% (Fig. 3). This volume variation is the result of volume decrease of the proximal tubular cells, and a slight decrease of the interstitial volume with a simultaneous luminal dilatation in all tubules and in the distal tubular cells (Fig. 4). These instant volume changes are clear reflections of the heavy osmotic load created by the contrast medium (Fig. 2B).

Between 30 to 60 seconds after injection, the renal cortex of the rat decreases in volume below the pre-urographic level (Fig. 3). This decrease is the sum of a relative volume decrease of the proximal tubular compartment, and simultaneous increase of the share of the distal tubules and the interstitial space. Analysing Fig. 5 it is obvious that the decrease of the proximal tubular compartment is caused by both cellular and luminal changes. At three minutes an increase of cortical volume of 5% above the control volumes was seen. This increase is brought about by an increased volume share of both the proximal and distal tubules, and a decrease of the interstitial space (Fig. 4). The further observations 6 and 15 minutes after injection show a clear tendency in all compartments and fractions to a return to the control volumes. However, in none of the animals were the control volumes of the different cortical compartments entirely re-established. Yet the fluctuations of the different volume shares at this period were so small that their significance is doubtful. The present work shows that the great fluctuations of the renal cortical volume in rats come to an end within three minutes after the i.v. injection, followed by a tendency to re-establish the pre-urographic volumes in all cortical compartments and fractions. Thus we can conclude that in using renal size variations during urography for diagnosis of reno-vascular hypertension or other generalized cortical lesions, the most significant observations ought to be made during the very rapid initial changes after the i.v. injection of the contrast medium.

ACKNOWLEDGMENTS

The authors are grateful to Astra-Sjuko Co. Denmark for supplying the contrast medium and Mr. J. Henningsen M.Sc. for the statistical work.

REFERENCES

BØRDALEN, B. E., HAGBARTH, W., and HOLTERMANN, H., 1970. Osmotic properties of some contrast media. *Investigative Radiology*, *5*, 559–565.

CRAMER, B. M., and HEGEDÜS, V., 1977. Relationship between renal lymph flow and changes in kidney size during urography. *Investigative Radiology*, *12*, 251–255.

DORPH, S., and ØJGAARD, A., 1973a. Variations in size of the normal kidney following intravenous administration of water-soluble contrast medium and urea. *British Journal of Radiology*, *46*, 183–186.

1973b. Variations in renal size in the diagnosis of reno-vascular hypertension. *British Journal of Radiology*, *46*, 187–190.

1975. Renal distention in response to water-soluble contrast medium and various diuretics. *Scandinavien Journal of Urology and Nephrology*, *9*, 114–118.

DORPH, S., SOVAK, M., TALNER, L. B., and ROSEN, L., 1977. Why does kidney size change during i.v. urography. *Investigative Radiology*, *12*, 246–250.

FAARUP, P., SÆLAN, H., and RYØ, G., 1971. Correlation between tubules and capillaries and size of interstitial space in the functioning rat kidney. *Acta Pathalogica and Microbiologica Scandinavica Section A*, *79*, 607–616.

GOTTSCHALK, C. W., and MYLLE, M., 1957. Micropuncture study of pressures in proximal and distal tubules and pertitubular capillaries of the rat kidney during osmotic diuresis. *American Journal of Physiology*, *189*, 323–328.

HEGEDÜS, V., CRAMER, B. M., and COCKETT, T. K., 1974. Lymphatic distribution of intravenous radiographic contrast media. *Investigative Radiology*, *9*, 56–60.

HEGEDÜS, V., and FAARUP, P., 1972. Cortical volume of the normal human kidney. *Acta Radiologica Diagnosis*, *12*, 481–495.

LINDGREN, P., and SALTZMAN, G. F., 1974. Increase of subcapsular renal pressure after intravenous iodipamide and other parenteral contrast media. *Acta Radiologica Diagnosis*, *15*, 273–280.

SWANN, H. G., 1960. The functional distension of the kidney. *Texas Reports on Biology and Medicine*, *18*, 566–595.

Book review

Medical Radionuclide Imaging. Proceedings of a Symposium, Los Angeles October 25–29 1976. Vol. I pp. 617, vol. II pp. 476, with author index, 1977. (International Atomic Energy Agency, Vienna) Vol. I $43, Vol. II $33.

These volumes form the proceedings of the symposium organized by the International Atomic Energy Agency and held in Los Angeles in October, 1976, a meeting which some had tried hard to bring to the United Kingdom. This was the fifth symposium on the subject organized by the Agency; the first, held in Vienna in February, 1959, had 36 participants from 21 countries (Proceedings $4=24 shillings, hard covers pp. 266); the recent meeting had 276 participants and 80 observers from 27 countries. Just four persons, all well known personalities, were fortunate enough to have taken part in both meetings.

Volume I has seven main sections, covering quality control, detectors, tomography, instrumentation and data processing, complementary methods, image evaluation and reports on IAEA co-ordinated research programmes. Volume II has six main sections, dealing with radiopharmaceuticals, bone and bone-marrow, cardiac and various other organ studies, the social impact of nuclear medicine and dosimetry.

The papers are generally distinguished for the depth of the analyses presented; the extensive verbatim records of the discussions following each paper make excellent reading. Evidently there was much controversy; this is well illustrated by the arguments between speakers over a paper by C. S. B. Galasko on the interpretation of radionuclide studies of skeletal metastases, and the comparative roles of moving detectors and camera systems in studies of the physiology of regional cerebral circulation provoked lively exchanges between H. N. Wagner of Johns Hopkins and M. E. Phelps of UCLA.

The problems of comparing the performance of different imaging systems are considered in depth, with many examples of trials set up between different hospitals using a variety of test systems; the BIR publication, Special Report No. 9, is among the reports complimented. Towards the end of a large series of papers on this and related topics M. J. Myers asked "How much real notice is taken of the results of all these very careful and extensive studies? For example, has the decision been taken to give up the use of the colour scan for the photoscan or of the rectilinear scanner in favour of the camera?" The brief response recorded indicated that factors other than science are at work when choices between methods are being made.

The awareness of both organizers and participants of the high cost involved in current developments of radionuclide imaging techniques, and the implications in securing adequate support, came out in formal lectures and in comments made in many discussions. The evolution of tomographic systems, of increasing boldness in design and expense in manufacture, was a major topic of the symposium; speakers were evidently concerned to make a realistic appraisal of the equipment being developed and neither to underrate its potential nor to exaggerate what has so far been achieved in clinical applications. Several papers reported comparisons of radionuclide and other computer assisted tomographic systems; this led to the enunciation of Veall's law (p. 477, Vol. I) "Whenever a comparison is made between two techniques *e.g.* . . . radionuclide versus C T scanning. . . provided that the two techniques are not measuring the same thing, the conclusion is inevitably reached that the two methods are complementary" Cost-consciousness was also evident in the papers related to the role of cyclotrons (with the frequently voiced hope for a really economical "desk top" instrument), albeit enlivened by an emotional appeal by G. L. De Nardo and colleagues of the University of California School of Medicine and the Crocker Nuclear Laboratory for the merits of ^{123}I to be more widely recognized and the cost to the user reduced. Several papers dealt with developments in semi-conductor imaging devices but their ultimate place in clinical or laboratory imaging cannot yet be foreseen.

The comparatively few (15) participants from the U.K. (Sir Freddie Laker, where were you?) compensated for the paucity of their numbers by the extent of their contributions, and the proceedings conclude with a thoughtful 18 page invited review by Keith Britton on "Renal Radionuclide Techniques in their Clinical Content".

The paper on dosimetry by A. Kaul, H. D. Roedler and G. J. Hine very conveniently includes details of the biokinetic data on which the calculations of absorbed dose (expressed both in mrad/μCi and in μGy/MBq) are based.

The production of these two volumes maintains the high standards set by the IAEA in their previous publications in this field; they will each surely prove of continuing value as sources of technical information and ideas, both in the texts of the papers and the lively and informed discussions. At 20 times the cost of the 1959 publication in the series (but, perhaps surprisingly, only 50% greater than the proceedings of the 1972 Monaco meeting) sales to individual workers are likely to be few, but advisers to librarians, sometimes justifiably sceptical of the value of published reports of meetings, can urge that these proceedings will prove a good investment for their scientific and medical readers.

N. G. TROTT.

1978, *British Journal of Radiology*, *51*, 799–801

Contrast media during coronary arteriography: electrocardiographic changes in the presence of normal coronary arteries

By M. Kyriakidis, M.D., G. Jackson, M.B., M.R.C.P., and D. Jewitt, M.B., F.R.C.P.

Cardiac Department, King's College Hospital, London SE5 9RS

(*Received February, 1978*)

Abstract

In forty patients with normal coronary arteries, the electrocardiographic changes secondary to Urografin 76 and Hypaque 85 injection into both coronary arteries were monitored. Hypaque caused significantly greater prolongation of the PR interval ($p < 0.001$), depression of the ST segment ($p < 0.05$) and depth of T wave inversion ($p < 0.05$). These effects were more noticeable during right coronary artery injection. Both contrast media slowed the heart rate equally during right and left coronary artery injection.

In the absence of coronary arterial disease the ECG changes secondary to contrast media injection probably reflect a direct toxic effect. It is possible that premedication with atropine will reduce these effects. Urografin 76 appears the less toxic of the two media, although one case of ventricular fibrillation occurred with each.

The effects of contrast media injection on the electrocardiogram during coronary arteriography have been studied in dogs (Banks *et al.*, 1969; Yamazaki *et al.*, 1975; Tragardh *et al.*, 1976) and in man (Banks *et al.*, 1970; Verel *et al.*, 1975). The main change is a slowing of heart rate especially during right coronary artery injection but ventricular fibrillation is also known to occur (Gensini and DiGiorgi, 1964). Depression of the S-T segment and T wave inversion secondary to contrast injection was used as an indication of toxicity by Verel *et al.* (1975).

Contrast media used routinely for coronary arteriography are combinations of the sodium and meglumine salts of the tri-iodo benzoates. The incidence of ECG abnormalities and ventricular fibrillation decreases the closer the sodium concentration is to that of plasma (Paulin and Adams, 1971). Urografin 76 is in widespread use for coronary arteriography but the greater iodine content of Hypaque 85 produces better contrast. Studies of their toxicity in man could be influenced by the presence of significant valvar or coronary arterial disease. We have, therefore, studied the direct effects of both contrast media on the electrocardiogram in 40 patients whose coronary arteriograms were normal.

Patients and Methods

Forty patients with suspected coronary arterial disease, 24 males and 16 females, underwent coronary arteriography. They all received diazepam 10 mg as premedication but no cardio-active drugs. Angiographic pictures were of high quality and taken in several projections. All 40 patients had normal coronary arteries and left ventricular function. In addition, there was no angiographic or echocardiogram evidence of a cardiomyopathy and no conduction disturbances were recorded on the 12-lead electrocardiogram prior to catheterization. In 36 patients Judkins' technique (Judkins, 1967) was used and in the remaining four patients Sones' technique (Sones and Shirey, 1962). During none of the injections was spasm observed.

In 20 patients the contrast medium used was Hypaque 85 and in the other 20 Urografin 76. Hypaque 85 contains 0.44 g/ml iodine and is a mixture of 28.33% w/v sodium diatrizoate and 56.67% w/v meglumine salt of diatrizoic acid in aqueous solution. Urografin 76 contains 0.37 g/ml iodine and is a mixture of sodium diatrizoate and meglumine diatrizoate in a ratio of 10:66 in aqueous solution in a concentration of w/v 76%. The temperature of the contrast media was 30°C throughout the studies.

An ECG (lead II and V2) was recorded at a paper speed of 25 mm/sec immediately before, during and after every coronary artery injection. The traces were analysed in detail for changes in heart rate, P-R interval, QRS complex width, S-T segment depression, T wave inversion and dysrhythmias. Statistical analysis employed an analysis of variance.

Results

The electrocardiographic changes are summarized in Tables I and II. Heart rate was reduced during right or left coronary artery injection by both Hypaque and Urografin and there was no significant difference between them. During right coronary artery injection electrocardiographic changes were more pronounced, with Hypaque significantly prolonging the PR interval ($p < 0.001$) causing greater S-T segment depression ($p < 0.05$) and T wave inversion ($p < 0.05$) than Urografin. The PR interval was also prolonged by Hypaque during left coronary artery injection ($p < 0.01$) when compared with

TABLE I

Result of injection of contrast media. Right coronary artery.

	Number of patients	Mean changes with Hypaque 85	Mean changes with Urografin 76	Standard error	Significance
Heart rate	20	−13.3	−11.9	3.45	N.S.
P-R interval	20	+1.34	+0.26	0.273	$p<0.001$
QRS complex	20	+0.219	+0.189	0.1244	N.S.
ST segment	20	−0.395	−0.026	1.1865	$p<0.05$
T wave	20	−2.75	−0.04	0.118	$p<0.05$

TABLE II

Results of injection of contrast media. Left coronary artery

	Number of patients	Mean changes with Hypaque 85	Mean changes with Urografin 76	Standard error	Significance
Heart rate	20	−13.5	−10.2	3.22	N.S.
P-R interval	20	+0.73	+0.07	0.226	$p<0.01$
QRS complex	20	+0.155	+0.295	0.1177	N.S.
ST segment	20	−0.075	−0.310	0.1796	N.S.
T wave	20	+0.88	−1.02	1.215	N.S.

TABLE III

Number of patients with dysrhythmias following injection into the coronary arteries

	Right coronary injection		Left coronary injection	
	Hypaque 85	Urografin 76	Hypaque 85	Urografin 76
SV ectopics	2	—	—	—
Ventricular ectopics	—	3	3	3
Ventricular fibrillation	1	1	—	—
SA block	1	1	2	—
AV block	—	1	—	—

Changes in heart rate are expressed in beats per minute.
Changes in PR, QRS, S-T and T are expressed in mm.

Urografin. There was no significant difference between the effects of both contrast media on the QRS complex during either right or left coronary injection. Two patients (Table III) developed ventricular fibrillation during RCA injection, one with each contrast medium and both episodes followed a period of bradycardia.

Discussion

We have shown that even in the presence of normal coronary arteries contrast media have significant effects on the electrocardiogram. As in patients with coronary arterial disease injection into the right coronary artery appears more dangerous, inducing ventricular fibrillation in two of our patients.

The heart rate slowed significantly during both right and left coronary injection. These findings support the theories of Banks *et al.* (1970). They suggested the slowing was mediated by the vagus nerve because if a direct effect on the SA node was responsible a greater slowing would have been expected during RCA injection and this is not the case.

RCA injection is, however, associated with a greater prolongation of the PR interval than LCA injection, especially using Hypaque. As the arterial branch to the AV node normally arises from the RCA this probably reflects a direct toxic effect of the contrast medium on the A-V node as has been shown experimentally in dogs (Higgins, 1976).

The ST segment and T wave changes were more pronounced with Hypaque, again during RCA injection. These changes may be caused by ischaemia as the injection fills the coronary artery completely (Benchimol and McNally, 1966). The greater toxicity with RCA injection may reflect an increased susceptibility of right ventricular muscle to changes in oxygen saturation. However, there is some evidence that these ECG changes cannot be caused by hypoxia alone and are related to the ionic content of the media (Ovitt *et al.*, 1972).

While we agree with Banks *et al.* (1970) that Hypaque 85 provides better contrast we are disturbed by the more pronounced effects on the electrocardiogram. It appears that contrast medium injection is not without risk even in the presence of normal coronary arteries and normal left ventricular function. From the evidence we have presented, Urografin 76 is the less toxic. It may be that serious dysrhythmias are more likely to follow a period of severe bradycardia and a study of atropine premedication seems desirable.

REFERENCES

Banks, D. C., Raftery, E. B., and Oram, S., 1969. Evaluation of contrast media used in coronary arteriography. *British Heart Journal, 31*, 645–648.

1970. Evaluation of contrast media used in man for coronary arteriography. *British Heart Journal*, 32, 317–319.

Benchimol, A., and McNally, E. M., 1966. Haemodynamic and electrocardiographic effects of selective coronary angiography in man. *New England Journal of Medicine, 274*, 1217–1224.

Gensini, G. G., and DiGiorgi, S., 1964. Myocardial toxicity of contrast agents used in angiography. *Radiology, 82*, 24–34.

Higgins, Ch., 1976. Effects of contrast material on the conduction system of the heart: mechanism of action and identification of toxic component. (Abst.) *Circulation, 53–54*, 0151.

Judkins, M. P., 1967. Selective coronary arteriography. I. Percutaneous transfemoral technique. *Radiology, 89*, 815–824.

Ovitt, T., Rizik, G., Frech, R. S., Cramer, R., and Amplatz, K., 1972. Electrocardiographic changes in selective coronary arteriography; the importance of ions. *Radiology, 104*, 705–708.

Paulin, S., and Adams, D. F., 1971. Increased ventricular fibrillation during coronary arteriography with a new contrast medium preparation. *Radiology, 101*. 45–50.

Sones, F. M., and Shirey, E. K., 1962. Cinecoronary arteriography. *Modern Concepts of Cardiovascular Disease, 31*, 735–738.

Trägårdh, B., Lynch, P., and Tragardh, Monika, 1976. Coronary angiography with Diatrizoate and Metrizamide. *Acta Radiologica Diagnosis, 17*, 69–80.

Verel, D., Ward, C., and Aman, M., 1975. Comparison of Triosil 370 with Urografin 76 and Hypaque 65 for coronary arteriography. *British Heart Journal, 37*, 1049–1052.

Yamazaki, H., Aya, S., Horikawa, M., Matsumura, N., and Nakamura, Y., 1975. Effects of radiopaque material on coronary vascular reserve. *Japanese Heart Journal, 16*, 57–64.

Book reviews

Understanding Radiography. By S. H. Hiss, pp. xviii + 349 + index, illus., 1978 (Illinois, Charles C. Thomas), $29.50.

This expensive-looking and detailed book covers part of the radiographic photography syllabus for the Diploma of The College of Radiographers, with the addition of sections on secondary radiation grids and tomography. It dwells at length on the radiographic image and factors affecting it, such as intensifying screens, exposure factors, processing and control of scatter. To this end there are many reproductions of radiographs, some of which barely illustrate the point being made. In some cases they are reversed or upside down, serving more to confuse than enlighten the student.

The book deals usefully with processing and other film faults, and also includes a chapter as a guide to film critique.

Although the information in this book is available elsewhere, brought together in this way it could be useful to radiography students on a technical basis. Perhaps the all-embracing title is too broad for the limited scope of the book, considering the meaning given to the term "radiography" in this country. Absorption processes are well described, but the only other references to the human being are as a convenient conglomeration of flesh and bone and, even so, the author does not deal with positioning techniques. Surely a large part of "radiography" as we understand it is concerned with the patient as a person.

Jennifer Richmond.

Planning and Plutonium. Evidence of the Town and Country Planning Association to the public inquiry into an oxide reprocessing plant at Windscale, pp. xviii + 110, 1978. (Town and Country Planning Association, London) £2·00.

This book contains the prepared statements of witnesses speaking on behalf of the Town and Country Planning Association which was objecting to the proposed nuclear processing plant at Windscale. Three of the speakers were mainly concerned with the type of issue which is normal in planning enquiries, employment, housing, traffic and so on, one with future needs for electricity and three with radiological aspects, namely professors Rotblat and Ellis and Dr. Alice Stewart.

From the reader's point of view the only advantage of the book is its convenient format. The speakers' replies during cross-examination are not included. There is no mention of other objectors and of course nothing about the case of those supporting the application. As a minimum requirement the reader should also consult the report of Mr. Justice Parker to see where the Town and Country Planning Association's evidence fits into the general picture; this report is also published in a convenient format and is not appreciably longer. To find out what happened during cross-examination, and what the other witnesses said, it is necessary to consult the full transcript, a much more formidable undertaking.

D. K. Bewley.

1978, *British Journal of Radiology*, *51*, 802–807

Isotope renography and long term follow-up of renal transplant patients

By C. C. Doherty, M.D., M.R.C.P., J. F. Douglas, B.A., B.Cl., M.B., M.R.C.P., and Mary G. McGeown, M.D., Ph.D., F.R.C.P.*

Renal Unit, Belfast City Hospital, Belfast

(*Received January, 1978 and in revised form April, 1978*).

ABSTRACT

Isotope renography was carried out in 64 kidney transplant patients attending a follow-up clinic. Graft survival in these patients ranged from two months to ten years. Forty-one patients had normal renograms and 98% of these had satisfactory function (creatinine clearance greater than 50 ml/min). Eighteen patients showed a major renogram abnormality and 50% of these had impaired function. Five of these 18 have been explored and found to have graft complications (obstructive disease in four, chronic pyelonephritis in one). Exploration has not been undertaken in the remaining 13 but nine show evidence suggestive of graft pathology (proteinuria, impaired creatinine clearance, elevated urinary enzymes, calyceal distortion on IVP).

A successful kidney transplant should result in a normal isotope renogram, and a major abnormality of the renogram suggests the presence of a graft complication, even when the creatinine clearance is unimpaired. We feel renography is useful for identification of renal transplant patients who require further investigation or closer follow-up.

The isotope renogram was introduced in 1956 (Taplin *et al.*) and was first applied to assessment of renal transplant function in 1963 (Collins *et al.*). Authors concentrated on the immediate post-operative period (Kountz, *et al.*, 1965; Blaufox and Merrill, 1967) with emphasis on early detection of graft rejection (Awad, *et al.*, 1969; Moore and Hayes 1974). Less attention has been paid to the use of renography in long-term renal transplant patients, and this study examines renographic appearances in such patients in relation to the clinical picture and other tests of graft function.

MATERIALS AND METHODS

Patients

Sixty-four recipients of a cadaveric renal graft were studied. Fifty- seven had had bilateral nephrectomy before transplantation, and in the remaining seven serum creatinine levels were greater than 1320 μmol/l (15 mg/100 ml). All had required support by regular dialysis. Fifty-one patients had a graft survival time of two months to five years (79%) and the remaining 13 had survived from five to ten years (21%).

Immunosuppression was achieved with prednisone and azathioprine and renal function was assessed by regular measurement of urinary volume, blood urea, serum creatinine, creatinine clearance and urinary N-acetyl-B-D-glucosaminidase (NAG) levels. The following values were taken as evidence of normal graft function for a transplant patient on corticosteroid therapy:

24 hour urinary NAG less than 250 μmol.

serum creatinine less than 120 μmol/litre.

creatinine clearance consistently greater than 50 ml/min.

24 hour urinary protein less than 300 mg.

serum calcium less than 2·6 mmol/litre.

Renograms

No preparative dehydration or hydration was undertaken at the time of the test, and none of the patients were receiving drugs known to influence the renal handling of hippuran (penicillin, probenecid) or tubular sodium transport (thiazide diuretics). Informed consent was obtained from all patients prior to investigation.

A J&P MS 510 renographic system was used, comprising three sodium iodide detectors and collimators, analysing electronics and a multipoint recorder. The detector and collimator assembly allowed adjustment of the depth of the face of collimator from the detector, and also adjustment of the distance between the patient and the collimator. The method of computer-assisted subtraction of blood background (CASBB) was employed for all renograms to obtain the true kidney activity curve (Britton and Brown, 1971). Renography was performed in the supine position with the collimators placed over the graft in the iliac fossa, over the opposite iliac fossa and over the heart. The output from the subtraction unit was fed into a three-channel recorder which printed the signals as separate coloured numbers. The dose of radio-iodinated human serum albumin used was 10 μCi, and that of ^{131}I hippuran also 10 μCi.

Renograms were assessed by visual inspection and the following features were observed:

1. Time to peak
2. Slope of the second phase

---

*Requests for reprints to M. G. McGeown.

3. Sharpness of the peak
4. Rate of fall of the third phase.

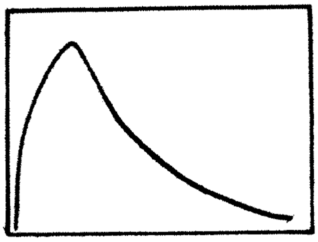
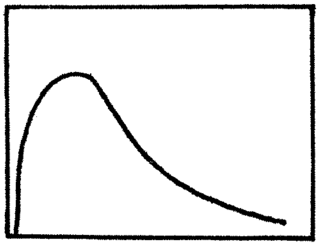
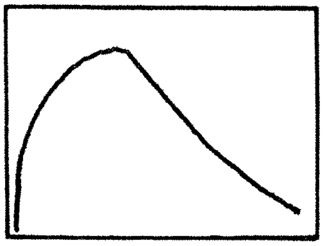
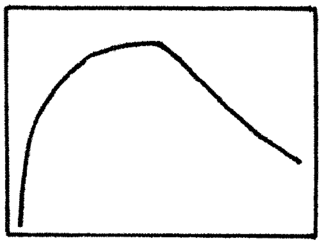
Renograms showing third phase irregularity as an isolated finding were not classified as abnormal. A cut-off peak or minimal delay in reaching the peak was classified as a minor renogram abnormality; all other changes were regarded as a major renogram abnormality. Patients who showed a markedly abnormal renogram were further evaluated by intravenous pyelogram (IVP) where appropriate, and some patients in addition had cystoscopy with retrograde ureteropyelogram, or open exploration of the graft with biopsy.

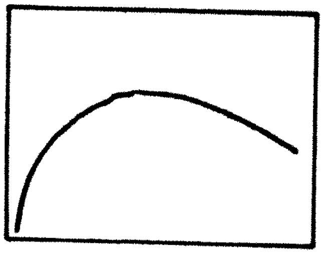
RESULTS

A number of different renogram patterns were seen, as illustrated diagrammatically in Fig. 1.

Patients with normal renograms

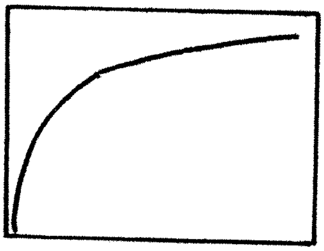
Forty-one patients (64%) showed a rapid rise to a sharp peak at two to four minutes, followed by

RENOGRAM		COMMENT
Normal (41 patients)		Graft function normal in 40
Minor Abnormality (a) Cut off peak (4 patients)		Suggests patchy parenchymal lesion
(b) Minimal delay in peak reached in 4–6 mins. (1 patient)		Urinary tract infection at time of renography
Major Abnormality (a) Broadened delayed peak (longer than 6 mins) with impaired second phase but good third phase fall (5 patients)		Chronic pyelonephritis proven in one patient



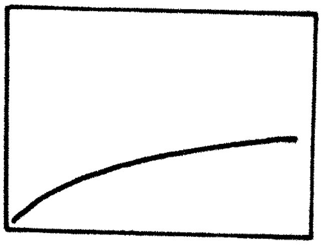
(b) Broadened delayed peak with impaired second and third phase (9 patients)

Obstructive nephropathy proven in 2 patients.



(c) Continuously rising curve with good second phase (2 patients)

Obstructive nephropathy proven in both patients



(d) Continuously rising curve with markedly impaired second phase (2 patients)

No diagnosis

FIG. 1.

Renogram appearances in 64 renal transplant patients.

gradually decreasing activity (Fig. 2). Ten of the 41 showed slight irregularity of the third phase as an isolated finding (Fig. 3).

Forty of the 41 patients with normal renograms (98%) had creatinine clearances consistantly greater than 50 ml/min. Other data at the time of investigation are given in Table I.

TABLE I.

CLINICAL DATA IN 41 RENAL TRANSPLANT PATIENTS WITH NORMAL RENOGRAMS

Number of patients	Clinical data*
23	No abnormal findings
7	Hypertension
3	Proteinuria
2	Hypertension and proteinuria
4	Hyperparathyroidism
1	Urinary tract infection
1	Mild impairment of function (serum creatinine 180 μmol/1)

*Includes clinical assessment, urine culture and microscopy, 24 hour urinary protein, 24 hour urinary NAG excretion, serum creatinine, creatinine clearance, serum calcium.

Patients with abnormal renograms

There was a major renogram abnormality in 18 patients (28%)*, but only nine showed impaired creatinine clearance. Five patients have had open exploration of the graft, of whom four were found to have obstructive nephropathy and one chronic pyelonephritis. Exploration has not been undertaken in the remaining 13 patients, but nine of the 13 showed other evidence suggestive of graft pathology (proteinuria, impaired creatinine clearance, elevated levels of urinary lysosomal enzymes, calyceal distortion on IVP).

Two patients who showed a major renogram abnormality but no impairment of creatinine clearance were found to have ureteric obstruction. The first of these two patients (see Fig.4) had surgical relief of the obstruction, with return of normal renographic appearances; his function remained unimpaired throughout. The second patient was not explored; fifteen months later, his graft function began to

---

*Further detailed information on these patients with abnormal renograms is available on request.

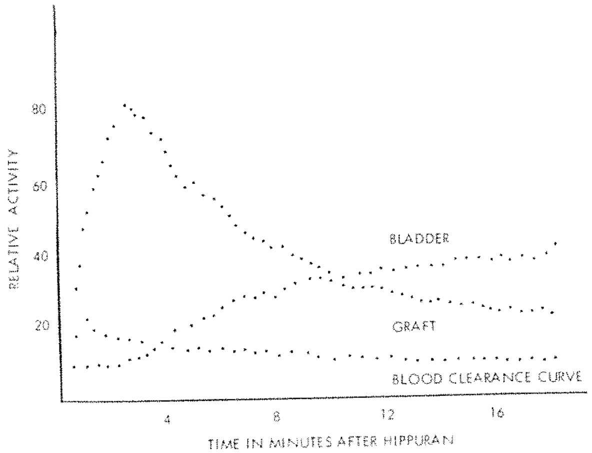


Fig. 2.

Type of renogram obtained in 41 of 64 patients with long-term renal transplants.
Age. 20. CASBB renogram three years post transplant. GFR 65 ml/min.
For clarity only the corrected curves are illustrated. The detector positioned over the opposite iliac fossa to the graft frequently picks up bladder activity and, as in this patient, a cystogram trace is obtained. The renogram shows a steep rise to a sharp peak within 4 minutes followed by a rapid fall-off. This is identical to the trace expected from a normal kidney.

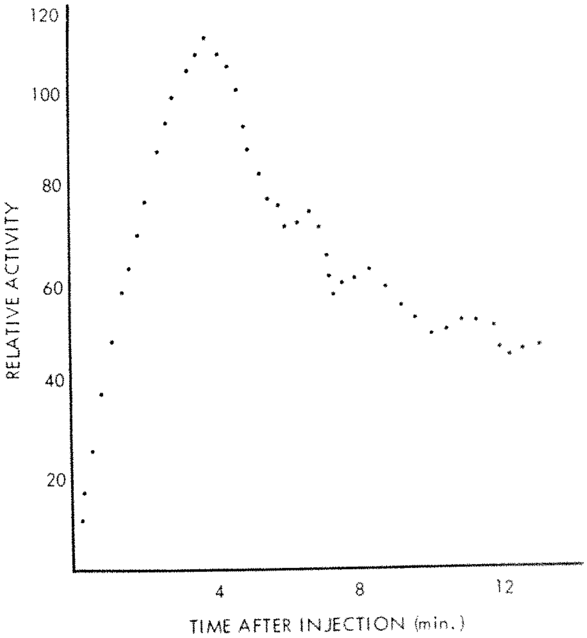
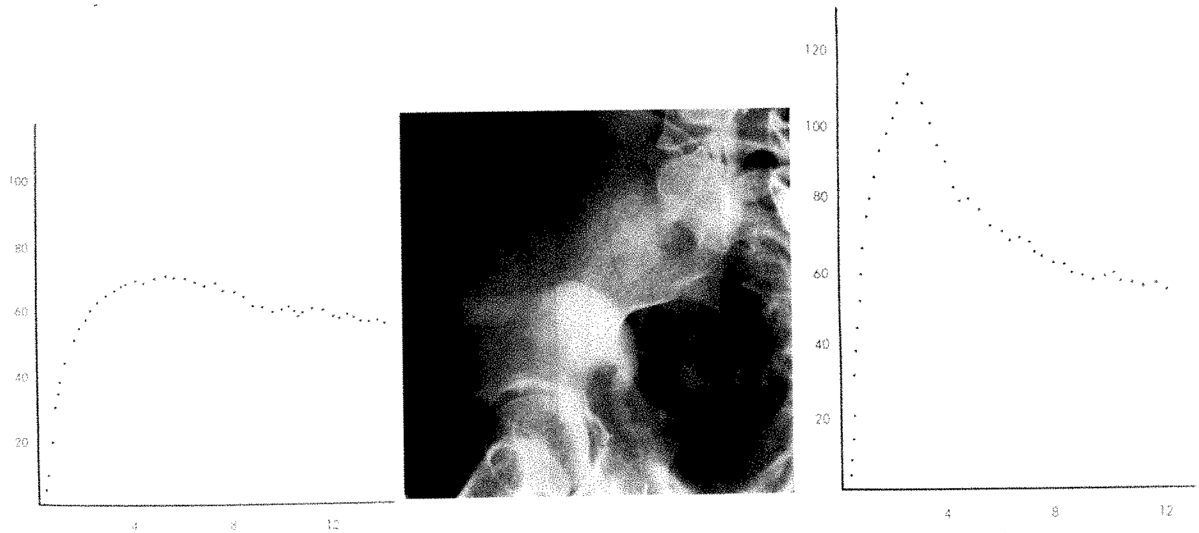


Fig. 3.

Renogram showing third phase irregularity as an isolated finding.
Age 39. CASBB renogram five years post transplant. GFR 108 ml/min.



(A) (B) (C)

Fig. 4.

Early obstructive nephropathy with normal creatinine clearance.

Age 38 years. Two years post-transplant. Normotensive. GFR 118 ml/min. No graft bruit. No proteinuria. Urinary NAG levels not elevated. (A) The renogram is abnormal, and when considered with the other negative findings is suggestive of early obstructive nephropathy. (B) IVP shows pelvi-calyceal dilation and vesico-ureteric obstruction. (C) The repeat renogram, four weeks after corrective surgery, shows a normal configuration.

decline and at operation he was found to have lower ureteric obstruction not apparent on the initial IVP.

The two other patients with obstructive nephropathy, who showed a major renogram abnormality had impairment of creatinine clearance. In both, corrective surgery was followed by return of normal renographic appearances and normal creatinine clearance.

Five patients (8%)* showed a renogram abnormality of minor nature, and none of these five showed impairment of creatinine clearance.

DISCUSSION

If a transplanted kidney has satisfactory arterial supply, urinary outflow and parenchymal function, then it is reasonable to expect that a radio-isotope renogram should not differ from that of a non-transplanted kidney. It has been stated however that the normal transplanted kidney has a delayed peak, and a third phase which falls more slowly than normal (Davies, 1976). In one study of 23 patients with stable transplant function, it was reported that 20 showed a renogram of normal overall configuration but with a delayed peak varying between 3·5 and eight minutes (Branch *et al.*, 1971). Hydrated normal subjects have a time to peak of between two and four minutes (Britton and Brown, 1971), and it was suggested that the delay may have reflected chronic rejection or other graft pathology. Opinions therefore differ regarding renogram appearances in long-term transplant patients. In the 64 patients studied here, 41 (64%) showed a completely normal configuration. The time to peak in the 41 patients varied between 2·5 and four minutes.

The isotope renogram should of course always be interpreted in association with other available clinical information, and abnormal findings were present in 18 of the 41 patients with normal renograms (see Table I). All of these findings were compatible with normal renal uptake and removal of hippuran.

The one patient with slight impairment of function had shown no change since the time of transplantation, (two years) and is considered to have a non-progressive lesion (*e.g.* a segmental infarct), consistent with a normal renogram. It may therefore be said that there were no false negative results.

Of the 18 patients who showed a major abnormality on the renogram, the underlying graft complication has been defined in five patients to date, and a further ten are considered to have graft pathology. No diagnosis has been reached in three patients who show a major abnormality of the renogram yet have no impairment of creatinine clearance or other detectable abnormality. It may be that the renographic appearances in these three patients are misleading, and are due to a reservoir effect; this could result from denervation of the transplanted kidney, rendering the pelvis liable to disordered activity and increase in physical size (due to loss of tone). If this is so, it may be said that these three results represent false positives among the 64 patients studied.

Irregularity of the third phase of the renogram was noted as an isolated finding in ten patients; there are several possible explanations for this. Abnormal ureteric peristalsis (Harvey and Keeling, 1969) and variation in renal blood flow (Britton, *et al.*, 1969) are both attractive suggestions. Pick-up of bladder activity by the detector looking at the graft may also affect the third phase, and in addition it may be that the transplanted ureter is liable to vesico-ureteric reflux.

Renography has been applied to the differential diagnosis of anuria occurring in the early post-transplant phase, and more recent studies have in addition used gamma camera scintiphotography (Hansen, *et al.*, 1976). We suggest that renography has also a place in long-term follow-up of renal transplant patients. A major renogram abnormality in a long-term renal transplant patient suggests the presence of a graft complication, and—especially in obstructive nephropathy—may precede any decline in creatinine clearance. In view of the frequency of obstruction as a late complication, there is a case for using the renogram as a screening test to identify patients who require further investigation or closer follow-up.

ACKNOWLEDGMENTS

We wish to express our gratitude to Mr. J. Kennedy, Mr. Stewart Clarke and Mr. G. Loughridge, consultant urological surgeons, who carried out the surgical investigation and treatment of these patients; and to the nursing, technical and secretarial staff of the Renal Unit, Belfast City Hospital for their assistance. We also thank Miss Mary Martin, secretary Royal Victoria Hospital, who typed the text.

The project was made possible by the Northern Ireland Kidney Research Foundation which provided the renographic apparatus used in the study.

REFERENCES

AWAD, W., BENNETT, L. R. and MARTIN, D. C., 1969. Detection of renal homograft rejection with a single dose of radiohippuran. *Journal of Urology*, *100*, 233.

BLAUFOX, D. M. and MERRILL, J. P., 1967. Evaluation of renal transplant function by iodohippurate sodium ^{131}I. *Journal of the American Medical Association 202*, 575–578.

BRANCH, R. A., COLES, G. A., EYNON, A., JONES, G. R. and LOWDER, E., 1971. The use of radioactive hippuran in the management of cadaveric renal transplants. *British Journal of Radiology*, *44*, 697–704.

---

*Further detailed information on these patients with abnormal renograms is available on request.

BRITTON, K. E., and BROWN, N. J. G., 1971 *Clinical Renography*. (Lloyd-Luke, London).

BRITTON, K. E., BROWN, N. V. G. and SLATER, J. D. H., 1969. Isotope renography. *Lancet*, 986.

COLLINS, J. J., PLZAK, L. F., TAMVAKOPOULOS, S. K. and WILSON, E. R., 1963. Serial renograms after kidney transplantation in man. *Surgical Forum*, *14*, 217–218.

DAVIES, E. R., 1976. Radioisotope studies of the kidney. *Urology*, *1*, Blandy, J. P. 117–137.

HARVEY, R. F. and KEELING, D. H., 1969. Investigation of ureteric function by isotope renography. *Lancet*, *1*, 847–850.

KOUNTZ, S. L., LAUB, D. R., and COHN, R. 1965. Detecting and treating early renal homotransplant rejection. *Journal of the American Medical Association*, *191*, 997–1001.

HANSEN, H. E., SKOV, P. E., HVID-HANSEN, H., SELL, A., TAAGEHØJ-JENSEN, J., ULSØ, N., 1976. In *Proceedings of the XIII European Dialysis and Transplant Association* (London, Pitman).

MOORE, T. C. and HAYES, M., 1974. Combined use of ^{131}I hippurate blood clearance and bladder/kidney ratio data in the early detection, classification and management of accelerated rejection of human renal transplants. *Surgery*, *76*, 587–600.

TAPLIN, G. V., MEREDITH, O. M., KADE, H. and WINTER, C. C., 1956. The radioisotope renogram. An external test for individual kidney function and upper urinery tract patency. *Journal of Laboratory and Clinical medicine*, *48*, 886–901.

Book review

Pediatric Radiology. Medical Outline Series. By Alan E. Oestreich, pp. 338 1977 (Henry Kimpton Publishers, London), £11·25.

Dr. Alan Oestreich has produced a modestly priced textbook filled with useful information presented in list form, but marred by unsatisfactory illustrations.

It is printed on good paper with clear type with a loose plastic ring binder. The X-ray reproductions are a disaster and the inclusion of two excellent line drawings dramatically illustrates what might have been achieved by replacement of all radiographs by drawings of this quality.

The opening chapter entitled " The Language of Radiology and Tracts" explains the form used throughout the text. The author divides the systems of the body into tracts and discusses each in terms of "Increase, Decrease and Outpouchings" followed by a discussion of "inflammatory diseases and other findings, sites and conditions".

The method, although difficult to follow, is adhered to strictly and results in numbered lists of facts, radiological and pathological, under headings derived from that terminology. The lists comprise words, phrases, sometimes short paragraphs.

The most important conditions encountered in paediatric radiology are dealt with together with a remarkable number of rarities used to illustrate particular points.

There is a good up-to-date list of references which does include some important European papers as well as those from American Journals.

The author directs the book towards a wide range of people from medical students, trainee paediatricians and radiologists, physicians who look at childrens' X-rays, family practitioners to "other health care personnel". This seems very ambitious—trainees in paediatric radiology, once they have mastered the format used, might find this book of value for revision purposes if used in association with a good film museum. They would be most unwise to waste time puzzling over the illustrations.

ELIZABETH M. SWEET.

1978, *British Journal of Radiology*, *51*, 808–813

The tolerance of mouse tails to necrosis after repeated irradiation with X rays

By J. H. Hendry, Ph.D.

Paterson Laboratories, Christie Hospital & Holt Radium Institute, Manchester M20 9BX

(*Received January, 1978 and in revised form April, 1978*)

Abstract

The reduction in the "tolerance" dose for the production of tail necrosis in adult mice seven weeks after irradiation has been measured in tails which had previously received various single or multiple tolerable doses. The major findings are:

A. The ability of heavily-irradiated and healed tails to tolerate about a further 90% of the first dose was found to apply between six weeks and ten months after the first irradiation.

B. The tolerance dose was reduced to about 65% of the original at the third irradiation, and this dose (approximately) remained tolerable at the fourth, fifth and sixth irradiation, all delivered at six week intervals.

C. Subsequent to seven weeks after the sixth dose, late effects were observed as an atrophy of the tail, mostly distal to the healed irradiated region. The occurrence was very marked (occurring in about 40% of tails by eight months) compared with that observed after only one dose (not more than 4% by eight months). Hence, if the assay time was extended to eight months after irradiation to include these late effects, the tolerance dose for the tail after the sixth dose would be reduced further to about 55% of the original value.

Residual damage in irradiated normal tissue is receiving increasing attention from radiobiologists owing to the use of adjuvants in radiotherapy, such as chemotherapeutic agents, which may modify normal tissue response. Several recent reports have shown that little residual damage is observed in rodent skin, as evidenced by the ability of the heavily-irradiated tissue to tolerate up to about a further 90% of the initial dose, when sufficient time is allowed for the early reactions to subside. This finding is of interest with respect to the ability of tissues to shed radiation damage and it is somewhat contrary to clinical expectations. Experiments are reported here, using the mouse-tail necrosis assay, to investigate the response to re-irradiation as a function of dose in, and time after, the initial treatment. Single and multiple tolerable doses were also studied.

Materials and Methods

Unanaesthetized female B6D2F$_1$ mice were used throughout; they were 10–12 weeks of age at the start of the experiments. Irradiation of a 2 cm (or as specified) length of mid-tail was performed using 300 kV X rays, with the tails in air at ambient temperature (21–25°C) or at 37°C, as described previously (Hendry *et al.*, 1976). This raised environmental temperature was used in some experiments to increase the level of oxygenation of the tail tissue which is rather hypoxic radiobiologically at ambient temperature but less so at 37°C (Hendry, 1978). The ND$_{50}$, or the dose necessary to produce permanent tissue breakdown (necrosis) in 50% of tails by seven weeks after irradiation, was calculated using probit analysis (Hendry *et al.*, 1976; Hendry, 1978). Late necroses were noted up to eight months after irradiation in some experiments. These were observed either as deterioration of a small, poorly re-epithelialized region or more often as atrophy and subsequent loss of the distal portion of the tail. The atrophy was occasionally observed to begin at the distal end of the irradiated region, but in most cases it was progressive from the distal unirradiated end of the tail. Tissue recovery was assessed by the response to re-irradiation of the same region of tail (except where stated) and the additional dose required to reach the ND$_{50}$ was determined.

Results

Single re-irradiation

The time course of tissue recovery was determined by the additional dose necessary at 37°C to reach the ND$_{50}$ at various times after a first dose of 1500 rad (about half the ND$_{50}$). At days 1, 7, 14, 21 and 28 the additional doses were 2120 ± 110, ~2410, ~1600, ~2780 and 3180 ± 150 rad respectively. The latter value was similar to that observed for control tails which is included in Table I.

On the basis of the above time course after a first dose of 1500 rad, the dependence of the amount of

TABLE I

Dose-reductions at six weeks after priming doses at 37°C

Priming dose at 37°C (rad)	ND$_{50}$ at 37°C ± SE (rad)	ND$_{50}$ reduction factor ± SE
0	3200 ± 170	1.0
750	3260 ± 110	1.02 ± 0.06
1500	3180 ± 150*	0.99 ± 0.07
2100	2930 ± 50	0.92 ± 0.05
2750	~2840	~0.89

*Measured at four weeks.

recovery on the size of the first dose was measured by the additional dose necessary to reach the ND_{50} at six weeks after various first doses. The results are given in Table I and they demonstrate a trend towards a lack of full recovery only at first doses higher than about half the ND_{50}. The further time course of response to re-irradiation, up to ten months after a large first dose of 4000 rad given at ambient temperature (about 0.9 ND_{50}), is shown in Table II. The small reduction in ND_{50} for both control and pre-irradiated tails at six and eight months is associated with the increased ambient temperature at those times (see discussion).

The small proportion of late necroses developing after the assay at week seven was unfortunately not noted in these experiments. However, an upper limit to this proportion is given by the number of tails re-irradiated at eight or ten months in comparison with the number given the first dose. The upper limits are 4% by eight months and 11% by ten months after the first dose, and these values include the proportion necrosing by week seven post-irradiation. Both values are even lower than the average value of 28% of tails necrosing by week six after the first irradiation of 4000 rad in experiments A, B and C described in the next section. Thus the true values for late necroses between week seven and either eight or ten months are likely to be much lower than the above upper limits. Apart from these late effects, both the ND_{50} for control tails and the minor reduction in ND_{50} after pre-irradiation show little change up to ten months after the first dose.

The response to re-irradiation as a function of the initial treatment is shown for several conditions in Table III, where the second irradiation was delivered to a 2 cm length of tail in air at ambient temperature. The time interval between the first and second irradiation varied, but for intervals greater than six weeks this is not critical, as shown above. Previous values are included for completeness. For the new data, the initial treatments consisted of a range of doses designed to bracket the ND_{50} and thus the mean dose to survivors of the first treatment was just less than the ND_{50}. There was an indication that a smaller dose was required at re-irradiation when a greater length of tail was irradiated in the first treatment (see lower half of Table III). After a first dose of 10 MeV electrons, the ND_{50} at the subsequent irradiation with X rays was reduced to about 0.9 of the original value, as after a first dose of X rays. Re-treatment under severely hypoxic conditions using a tail clamp—although performed later after the first dose than irradiations without a clamp—showed a ratio of about 1.7 with respect to the ND_{50} in air.

TABLE II

REDUCTION IN ND_{50} FOR RE-IRRADIATION AT DIFFERENT TIMES AFTER A FIRST DOSE OF 4000 RAD AT AMBIENT TEMPERATURE (21–25°C)

Time after priming dose	ND_{50} ± SE (rad)		ND_{50} reduction factor ± SE
	controls	after pre-irradiation	
5–6 weeks	4580 ± 120	4450 ± 260	0.97 ± 0.06
3 months	4350 ± 110	4450 ± 130	1.02 ± 0.04
6 months*	3780 ± 220	3850 ± 190	1.02 ± 0.08
8 months*	4100 ± 90	3910 ± 80	0.95 ± 0.03
10 months	4220 ± 100	~4040	~0.96

*29°C ambient temperature.

TABLE III

REDUCTION IN ND_{50} FOR RE-IRRADIATION WITH X RAYS IN AIR AT AMBIENT TEMPERATURE (except b) AFTER VARIOUS FIRST IRRADIATIONS GIVEN TO UNCLAMPED TAILS. DOSES AT THE FIRST IRRADIATION WERE A MEASURED FRACTION OF ND_{50} (UPPER HALF OF TABLE) OR A RANGE OF DOSES BRACKETING ND_{50} (LOWER HALF OF TABLE)

First irradiation			Time interval (weeks)	Second ND_{50} ± SE (rad)	ND_{50} reduction factor ± SE
Tail length	Dose	Radiation			
2 cm	~0.9 ND_{50}	300 kV X ray	17–30	—	0.89 ± 0.02[a]
2 cm	0.86 ND_{50}	300 kV X ray	6	—	0.89[b]
2 cm	0.87 ND_{50}	300 kV X ray	5–6	—	0.97 ± 0.06[c]
—	—	—	—	4400 ± 40[d]	1.0
4.25 cm	—	300 kV X ray	8	3630 ± 160	0.83 ± 0.04
Whole tail	—	300 kV X ray	6	~3200	~0.73
2 cm	—	10 MeV electrons	6	3830 ± 110	0.87 ± 0.03
			10	6690 ± 390 (clamped)	—

[a]from Hendry *et al.* (1977); [b]from Table I; [c]from Table II; [d]from Hendry (1978).

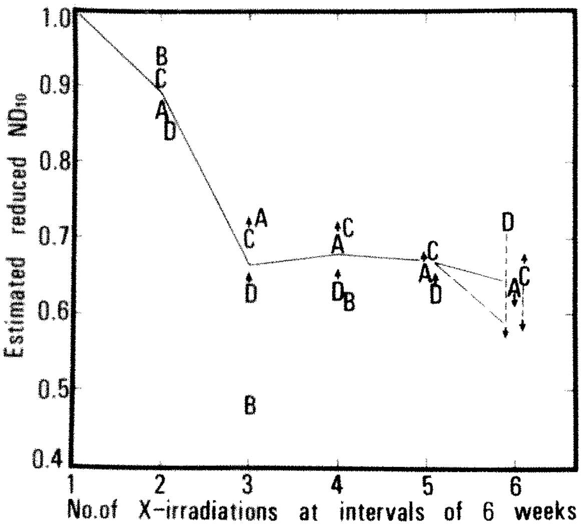


Fig. 1.

Estimated reduction in ND_{10} for each subsequent irradiation. A, B, C—irradiations at ambient temperature. D—irradiations at 37°C. Arrows—upper or lower limits to values (see text). Dotted arrows—reduction in values due to late necroses, so reducing ND_{10} further (dashed line).

Multiple irradiations

Four experiments were performed with repeated irradiation of tails every six weeks to roughly ND_{10} levels (an upper limit to "tolerance" levels—Hendry *et al.*, 1976). The results are shown in Fig. 1. In each experiment, 50–60 mouse tails received 4000 rad of X rays at ambient temperature (experiments A, B and C, Fig. 1), or 2600 rad at 37°C (experiment D, Fig. 1). At six weeks after the first dose, the fraction of necrotic tails was noted and the ND_{10} value was estimated using the comprehensive dose-reponse curve for necrosis presented previously (Hendry, 1978) for the mean of 11 replicate experiments. This procedure assumes that for all treatments the slope of the dose-response curve does not change so as to alter significantly the extrapolation from ND_{measured} to ND_{10}. The remaining fraction of tails was re-irradiated with the previous dose reduced by 10% (*e.g.* 3600 rad, see above), based on previous estimates (top, Table III). A similar procedure was adopted for each irradiation, up to a maximum of six in these experiments, and the doses were reduced progressively by retrospective estimates. When no tail necrosed in a group, a lower limit to ND_{10} is shown in Fig. 1 by the upright arrows and similarly for all tails necrosing by the downward-pointing arrow. Those tails which had not necrosed by seven weeks after the sixth irradiation were kept for a further eight weeks to assess any late development of damage. Sufficient numbers for assessment were available only in experiments C and D. In C, no tails necrosed by seven weeks after the chosen sixth dose, but 1/19 atrophied by six months and a further 6/18 by eight months. These late effects changed the estimated ND_{10} from more than 0.65 ND_{10} (seven weeks) to 0.67 ND_{10} (six months) and to 0.58 ND_{10} (eight months), as shown in Fig. 1 by the dashed arrow. In D, 2/30 necrosed by seven weeks after the chosen sixth dose, followed by a further loss of nine by six months, and a further three by eight months. This reduced the ND_{10} from 0.72 ND_{10} (seven weeks) to 0.60 ND_{10} (six months) and to 0.57 ND_{10} (eight months) as shown by another dashed arrow in Fig. 1.

Discussion

Single re-irradiation

The increase in dose necessary to reach the ND_{50} at day one after 1500 rad provides a value for (D_2-D_1)* of about 650 rad and this is similar to the value of about 600 rad reported previously for ND_{50} in rat tails (Hendry *et al.*, 1976), and to values between 525 and 700 rad for skin reactions in mice, pigs and humans. The further daily increases in dose required to achieve 50% necrosis are about 48 rad/day during week one and about 27, 26 and 58 rad/day during weeks two, three and four respectively. These are within the range of values reported by others for various skin reactions with a mean of about 30 rad/day. The remarkable ability of this tissue to withstand a second treatment of magnitude 0.9 of the ND_{50} for a single dose (Table III), even after a high initial dose (ND_{10}), confirms the previous report for the tails of rats and mice (Hendry *et al.*, 1977), and reports of other investigators for skin reactions on mouse legs (Denekamp, 1975; Brown and Probert, 1975), rat ears (Field and Law, 1976) and human skin many years after high doses (Hunter and Stewart, 1977). All of these measurements contrast with the dosage reduction of about 40% for re-irradiation of mouse legs to achieve tolerance in terms of deformity (Brown and Probert, 1975), although this was not confirmed in subseqent similar experiments (Denekamp, 1977). Also shown here is the dose-dependence for the residual injury (Table I), and the near-constancy of the effect between six weeks and ten months post-irradiation (Table II). The latter is similar to the finding of Brown and Probert (1975) for both early reactions and late deformity. The greater sensitivity at six and eight months (Table II) is compatible with the higher ambient temperature and the known decrease in ND_{50} of about 90 rad per 1°C rise in air temperature due largely to increased oxygenation (Hendry, 1978). The effect of irradiated surrounding tissue on the response of the retreated volume is shown by the reduced ND_{50} after pre-irradiation of longer lengths (bottom half of Table III). The similarity of the ND_{50} reduction factors measured after first treatments with 10 MeV electrons or 300 kV X rays (Table III) indicates that residual injury after these two types of radiation is similar, after allowing for the RBE of the first doses (Williams and Hendry, 1978). This contrasts with previous measurements of residual injury after high LET radiation, where the ND_{50} at re-irradiation was reduced more after prior irradiation with neutrons than with X rays (Hendry *et al.*, 1977).

---

*Increase in total dose necessary for equivalent effect when a single dose is split into two equal fractions separated by 24 hours.

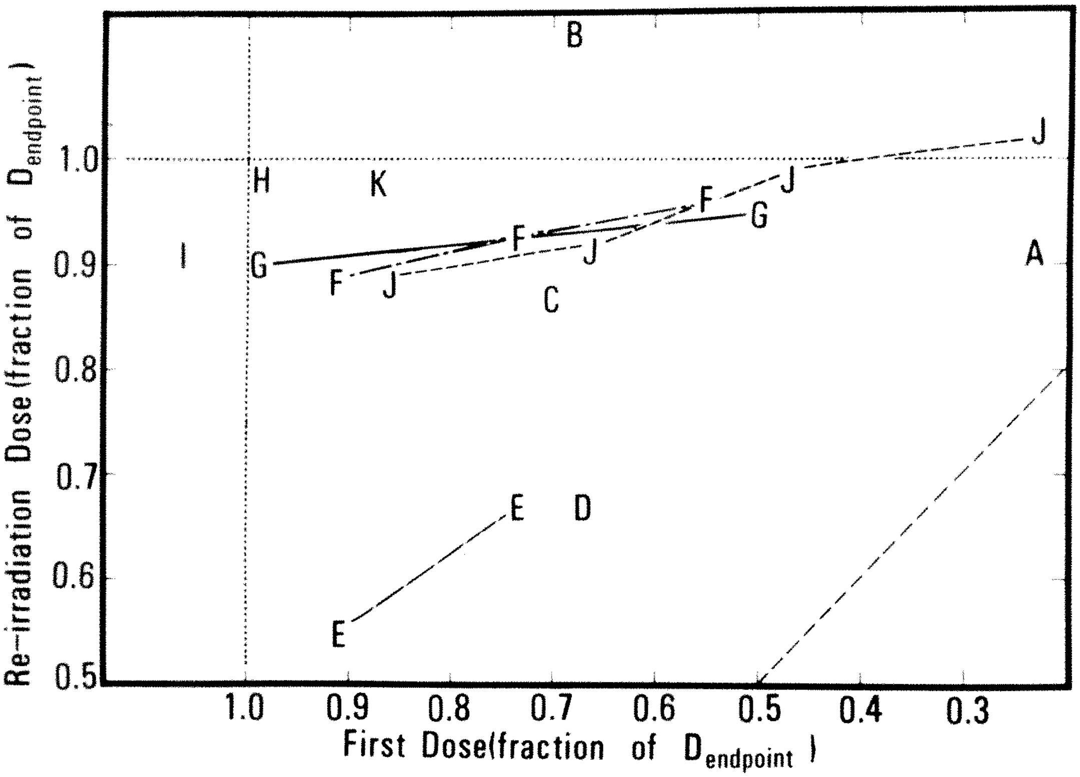
Multiple irradiations

The estimated ND_{10} is reduced to about 0.9 of the original at the second irradiation and to about 0.65 at the third. Thereafter, the value does not decrease significantly to the sixth irradiation. Changes in oxygenation are unlikely to contribute significantly to these findings, as the dose reductions are similar for experiment D (irradiations at 37°C with good oxygenation) and for experiments A to C (at ambient temperature with relatively poor oxygenation judged radiobiologically). Also, after a first dose of 10 MeV electrons, the ratio of dose of 1.7 for the second irradiation with X rays (at ambient temperature) in anoxic conditions to that in air (Table III) is similar to a previous measurement of 1.59 ± 0.04 at six months after a prior irradiation with X rays (Hendry *et al.*, 1977). Both values are near that of 1.54 ± 0.04 measured in control tails (Hendry *et al.*, 1976).

The incidence of late effects after the sixth dose is greater than after the first. The values to be compared are 4% by six months after the first tolerance dose (Hendry *et al.*, 1976) and 5% (experiment C) and 32% (experiment D) after the sixth. By eight months, the corresponding values are not more than 4% after the first, and 37% (C) and 43% (D) after the sixth. The latter values of course include the percentages of late necroses accrued by 15½ months after the first dose and by 14 months after the second dose, etc. However, the data necessary to assess these contributions fully are not available. Their importance is shown by the fact that a further 7% atrophied between eight and ten months after a first dose (see results section). Also, in previous work with rat tails, late necroses measured six months after re-irradiation at six months, *i.e.* by 12 months after the first dose, were not more than 3% and additional to the 4% measured by six months after the first dose (Hendry *et al.*, 1977). In general, any damage from the first dose which manifests itself between the second dose and the subsequent assay will tend to provide an overestimate of the effects of the second dose. With this proviso, these results confirm the findings of Brown and Probert (1975) of a greater effect of re-irradiation on very late damage than on early or mid-term damage, compared with the effects of a single irradiation. However, it should be noted that the total doses for the multiple irradiations employed here were very high, 18000 rad (experiment C) and 12000 rad (experiment D) spread over six treatments near tolerance. Thus, after only the second treatment the above-mentioned greater effect on late damage may not be very marked and may be undetectable, as noted for rat tails (quoted above) and for the relationship between early skin reactions and late deformity of rat ears after a first or after a second irradiation (Field and Law, 1976). The comparison of experiments C and D, where the tolerance doses in D were about two thirds of those in C due to temperature (and oxygenation status), demonstrated that in D there was no reduction in the frequency of the late effects for equivalent initial necroses—indeed, the trend is the other way. This indicates that the two expressions of damage are either causally related or that the different target cells are near each other and similarly affected by temperature and consequent changes in oxygenation. The former possibility is not supported by the increased late effects observed after the sixth dose, compared with the effects after a single dose.

Other tissues

The variation in the response to re-irradiation between different types of tissue is shown in Fig. 2, as deduced from a number of published experiments. The first dose, as a fraction of the dose necessary for a given endpoint, *e.g.* LD_{50}, is plotted against the second dose necessary to reach the same endpoint at re-irradiation. In general, the values are given for the longest time interval quoted, and the dashed line represents the addition of first and second doses to give unity. For all values of the first dose, the second dose is seen to lie above the dotted line. This is to be expected due to recovery from sub-lethal injury (Elkind repair) and any further "slow" repair (Field *et al.*, 1976). Tissues capable of marked repopulation, *e.g.* epithelial and haemopoietic tissues, will show even greater values for the second dose. Thus, the tissue element(s) in the rodent responsible for death after irradiation of the lungs (D, Fig. 2) are



Notation	Endpoint	Time interval	Reference
A	$LD_{50/30}$ (mouse)	3 weeks	Porteous and Lajtha, 1966
B	$LD_{50/30}$ (dog)	20 days	Ainsworth *et al.*, 1966
C	$LD_{50/60}$ (sheep)	1 month	Hanks *et al.*, 1966
D	$LD_{50/80}$ (mouse lung)	4 weeks	Field *et al.*, 1976
E	Tolerance for deformity of mouse leg	6 months	Brown and Probert, 1973
F	Average skin reaction in mouse leg of 1.4	6 months	Brown and Probert, 1975
G	Average skin reaction in mouse foot of 1.5 or foot deformity	6 months	Denekamp, 1975, 1977
H	Tolerance for deformity of rat ear	8 months	Field and Law, 1976
I	Rat tail necrosis—ND_{50}	6 months	Hendry *et al.*, 1977
J	Mouse tail necrosis—ND_{50}	6 weeks	Table I, this paper
K	Mouse tail necrosis—ND_{50}	6 weeks– 10 months	Table II, this paper

Fig. 2.

The additional dose required at re-irradiation after various first doses to reach the chosen endpoint. Doses expressed as a fraction of the single dose required to produce the endpoint, *e.g.* LD_{50}. Dashed line, lower right—simple addition of first and second doses.

probably examples of minimally repopulating tissues. Also, with local rather than whole-body irradiations, there may be enhanced recovery if migration of cells occurs from unirradiated regions, for instance when skin epithelium or bone marrow are irradiated with small fields.

Control values will only be reached at re-irradiation if the number of target cells is restored, if their sensitivity and functional capability are unimpaired, and if the supportive environment remains optimal. These factors have been investigated in detail only for mouse bone-marrow. After a large single dose, repopulation restores the number of stem cells nearly to the normal level (Guzman and Lajtha, 1970), but after repeated irradiation the number reaches only one tenth of normal and a cellular defect has been identified after subsequent grafting (Hendry *et al.*, 1974).

ACKNOWLEDGMENTS

I thank Mrs. Marion M. Brown for much technical assistance and Drs. R. D. Hunter, J. V. Moore, D. Greene and Professor L. G. Lajtha for their helpful comments.

This work was supported by grants from the Medical Research Council and the Cancer Research Campaign.

REFERENCES

AINSWORTH, E. J., and LEONG, G. F., 1966. Recovery from radiation injury in dogs as evaluated by the split-dose technique. *Radiation Research*, *29*, 131–142.

BROWN, M. J., and PROBERT, J. C., 1973. Long term recovery of connective tissue after irradiation. *Radiology*, *108*, 205–207

1975. Early and late radiation changes following a second course of irradiation. *Radiology*, *115*, 711–716.

DENEKAMP, J., 1975. Residual radiation damage in mouse skin 5–8 months after irradiation. *Radiology*, *115*, 191–195.

1977. Early and late radiation reactions in mouse feet. *British Journal of Cancer*, *36*, 322–329.

FIELD, S. B., HORNSEY, S., and KUTSUTANI, Y., 1976. Effects of fractionated irradiation on mouse lung and a phenomenon of slow repair. *British Journal of Radiology*, *49*, 700–707.

FIELD, S. B., and LAW, M. P., 1976. The relationship between early and late damage to rodents' skin. *International Journal of Radiation Biology*, *30*, 557–564.

GUZMAN, E., and LAJTHA, L. G., 1970. Some comparisons of the kinetic properties of femoral and splenic haemopoietic stem cells. *Cell and Tissue Kinetics*, *3*, 91–98.

HANKS, G. E., PAGE, N. P., AINSWORTH, E. J., LEONG, G. F., MENKES, C. K., and ALPEN, E. L., 1966. Acute mortality and recovery studies in sheep irradiated with Cobalt-60 gamma rays or 1-Mvp X rays. *Radiation Research*, *27*, 397–405.

HENDRY, J. H., TESTA, N. G., and LAJTHA, L. G., 1974. Effect of repeated doses of X rays or 14 MeV neutrons on mouse bone marrow. *Radiation Research*, *59*, 645–652.

HENDRY, J. H., ROSENBERG, I., GREENE, D., and STEWART, J. G., 1976. Tolerance of rodent tails to necrosis after 'daily' fractionated X rays or D-T neutrons. *British Journal of Radiology*, *49*, 690–699.

1977. Re-irradiation of rat tails to necrosis at 6 months after treatment with a 'tolerance' dose of X rays or neutrons. *British Journal of Radiology*, *50*, 567–572.

HENDRY, J. H., 1978. Radionecrosis of normal tissue: studies on mouse tails. *International Journal of Radiation Biology*, *33*, 47–55.

HUNTER, R. D., and STEWART, J. G., 1977. The tolerance to re-irradiation of heavily irradiated human skin. *British Journal of Radiology*, *50*, 573–575.

PORTEOUS, D. D., and LAJTHA, L. G., 1966. On stem cell recovery after irradiation. *British Journal of Haematology*, *12*, 177–188.

WILLIAMS, P. C., and HENDRY, J. H., The RBE of megavoltage photon and electron beams. *British Journal of Radiology*, *51*, 220.

Book review

Advanced Exercises in Diagnostic Radiology. No. 10: The Urinary Tract. By A. Walsh and J. G. McNulty, pp. viii+104, illus., 1977 (W. B. Saunders Co. Philadelphia, London, Toronto), £6·00.

This slim paperback volume is the tenth in a growing series which has rightly gained widespread popularity as an introduction to the problems and value of diagnostic radiology. Although termed advanced, it would seem to be aimed at the senior medical student and newly qualified practitioner. A series of cases illustrating relatively common problems in diagnostic uro-radiology are presented in a rather racy style. In each case a brief clinical picture and a radiological investigation precede an appropriate question. This is answered on the following page and when necessary, supported by further illustrations. Diagnostic ultrasound and isotope techniques have been omitted deliberately because these have been the subject of earlier volumes.

Although generously illustrated, the quality of reproduction is of a disappointingly low standard. In many cases an enlargement of the relevant portion of the film would have been advantageous and there is in the book ample blank space which could have been used for this purpose. It will be a source of regret to radiologists who read this volume that no emphasis has been placed upon the merit of discussing the case with a radiologist or of modifying the initial investigation in a manner appropriate to the presenting diagnostic problem.

Students who enjoy the question and answer presentation will undoubtedly enjoy this book and benefit from its study. It not only encourages an intelligent use of diagnostic radiology, but hopefully, may also stimulate serious consideration of radiology as a career. It can be thoroughly recommended, with the other volumes in the series, to all academic departments of diagnostic radiology.

J. ROYLANCE.

1978, *British Journal of Radiology*, *51*, 814–820

Iridium-192 afterloaded implant in the retreatment of head and neck cancers

By A. M. Nisar Syed, M.D., F.R.C.S., B. H. Feder, M.D., F.A.C.R.,
F. W. George III, M.D., F.A.C.R., and D. Neblett, B.S.E.E.

Radiation Medicine and Radiation Physics Sections, Los Angeles County – University of Southern
California Medical Center, 1200 North State Street, Los Angeles, California 90033, U.S.A.

(*Received October, 1977 and in revised form February, 1978*)

ABSTRACT

Retreatment of persistent (or "recurrent") carcinoma of the head and neck by means of after-loading ^{192}Ir techniques may prove quite satisfactory. A total of 64 patients were retreated by these techniques from February, 1974 to October, 1975 at the Los Angeles County–University of Southern California Medical Center and the Southern California Cancer Center. Follow-up periods, averaging only 24 months (18 to 36 months), are too short for statistically significant evaluation of survival, but the "response rate" has been gratifying.

Only 11 of our 64 patients (17%) have shown no satisfactory response to re-irradiation by interstitial implant. Thirty-one of the 64 patients (49%) have had local control with "good palliation". Twenty-two of the 64 (34%) had at least 50% regression of tumour with "fair" palliation. Thus 83% have had satisfactory response to retreatment. A considerable number of these have survived to the date of this report. Whereas 36 of the 64 (56%) are now dead, 28 of the 64 otherwise hopeless patients (44%) were alive with at least local control of neoplastic disease. Nineteen (30%) have developed necrosis in the implant area (we consider this an acceptable complication rate in view of the poor prognosis of the patients involved in this report). Our experience leads us to believe that local tissue tolerance to retreatment by this afterloading ^{192}Ir technique is considerably better than that which would be anticipated for retreatment using external irradiation alone. The degree of palliation obtained appears better than that reported for surgery or for chemotherapy in similar studies.

About half of the patients treated for head and neck cancers present with persistent or "recurrent" local disease after the initial attempt at cure by surgery and/or irradiation, according to Axtell (*et al.* 1972). Management of these patients is rarely satisfactory. Fletcher (1974) points out that "... *radiation* for post-radiation recurrences following a full dosage is contraindicated since it will almost invariably cause necrosis and failure to control the disease ... A satisfactory result is not feasible ...". Gelinas and Fletcher (1973) report only 34 successful *surgical* salvages in 106 failures after irradiation. Sealey and Hellman (1972) report that, in their experience with intra-arterial chemotherapy in 39 patients with persistent disease *after irradiation*, they were "... uniformly unsuccessful in obtaining a response ...".

We have been concerned with the retreatment of similar patients with locally persistent or "recurrent" head and neck cancer after presumably definitive irradiation (plus in some cases more or less definitive surgery). We have treated 64 such patients with ^{192}Ir afterloading interstitial implant. Our findings to date lead us to believe that this may prove to be a desirable method for the management of such lesions.

METHODS AND MATERIALS

We have treated 64 patients who had persistent (or "residual") head and neck cancers at least four months after completion of unsuccessful irradiation to "full tolerance levels" (Table I). In 12 of the 64 patients referred to us there had also been an attempt at total excision. All were considered to have a very poor prognosis and to be essentially "unresectable". They were usually referred for palliative management. Treatment was directed toward local control of the tumour by one of several interstitial implant techniques as follows:

Plastic tube and button technique

The method of insertion is shown in Fig. 1.

(a) Hollow steel needles (17 gauge) are inserted throughout the volume of interest so that both ends of the needle present on the skin surface.

(b) Plastic afterloading tubes are threaded through the steel needles. (One end of the plastic tube is already sealed, with a plastic button affixed as anchor.)

(c) As the hollow steel needles are removed, the plastic tubes are left in their place.

(d) A second, snugly fitting, plastic button is pushed onto each plastic tube and brought relatively close to the skin in order to keep the tubes in place.

(e) The tubes are filled first with ribbons of inactive sources. Localization radiographs are made using orthogonal geometry. The tumour volume (volume of interest) is then marked on the radiographs. These films furnish the source locations for computerized calculations of the dose distribution.

Partially supported by US Public Health Service Grant No. 1 P01 CA 20665 from Centers Program of National Cancer Institute.

TABLE I

HEAD AND NECK CANCER FAILURES SUBMITTED TO RETREATMENT BY AFTERLOADING ^{192}IR IMPLANT

Site	No. of Patients	Initial external radiation dose (rad)	Failure after primary surgery and iirradation		Failure after external irradiation alone	
			Persistent* disease	Recurrent† disease	Persistent* disease	Recurrent† disease
Floor of mouth	7	6000–7000	0	2	1	4
Mobile tongue	6	5500–6000‡	0	0	1	5
Retromolar area	9	6000–6500	0	3	1	5
Base of tongue and vallecula	10	6000–6500	0	2	1	7
Soft palate and uvula	4	6000–7000	0	0	0	4
Lip	1	5500	0	0	1	0
Gum	1	6000	0	0	0	1
Buccal mucosa	2	6400	0	0	0	2
Posterior pharynx	2	6400	0	0	1	1
Antrum	1	6000	0	0	1	0
Neck masses	21	6000–7000	2	3	7	9
	64		2 (3%)	10 (15%)	14 (22%)	38 (60%)

*Never a total tumour regression.

†Reappearance of tumour (within the treatment area) after initial "total regression".

‡One patient had received a regular radium implant to an estimated 3000 rad plus external irradiation to 5500 rad. (None of the others had had interstitial therapy.)

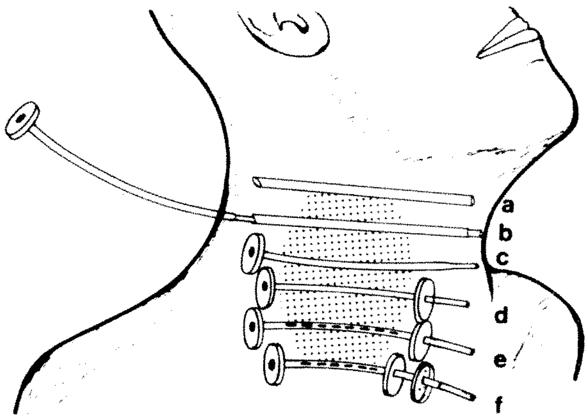


FIG. 1.

(a) Insertion of hollow needle; (b) threading of plastic tube; (c) removal of hollow needle; (d) fixation of plastic tube by plastic button; (e) placement of inactive sources for radiographs; (f) placement and fixation of active sources with steel button.

(f) The inactive sources are replaced by ribbons of active sources when the patient reaches his room. These sources are fixed in place by means of a steel button which is firmly crimped to occlude the lumen of the plastic tube.

Note: The iridium seeds used are cylinders of platinum-iridium wire covered with either a sheath of pure platinum or stainless steel, depending on the supplier. In either case the seeds are 3 mm long and 0.5 mm in diameter. The seeds are encased in plastic ribbons and fixed at regular intervals. Ribbons can be procured with seeds at varied intervals as necessary. The intervals between seeds usually measure 1 cm from centre to centre. (The techniques described are for these iridium seeds, but similar techniques could be employed with iridium wire.)

Computerized calculation of isodose distribution

Computerized calculation of the dose distribution is superior to the approximate methods of Paterson and Parker or Quimby. The computerized calculation provides more detailed information about dose distribution at selected points in the volume of interest. Furthermore, the complexity of the source geometry used in some implants defies both the Paterson-Parker distribution rules and the Quimby system (Fig. 2).

For each implant, two or more computer-generated isodose plots are made. The coordinates of each radioactive source from both orthogonal films are entered into the computer via a X–Y digitizing device. Selected planes are then calculated, point-by-point, with an algorithm which makes use of the inverse-square law and a tissue-to-air correction factor to account for scatter and attenuation in the volume, as described by Meredith *et al.* (1966) and Mohan (1975). These isodose plots are normally printed on special transparent paper at the same magnification and orientation as the localization radiographs. These transparent plots are then overlayed on the radiographs, and the dose distribution relative to the marked tumour volume mentioned above is reviewed by the physician and physicist. At

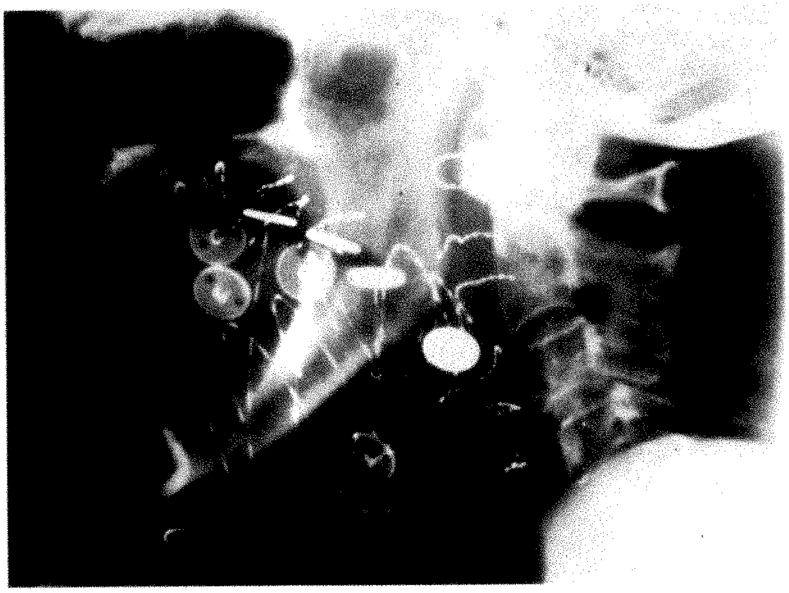


FIG. 2.

Relatively complex implant of retromolar trigone lesion which extends into postero-lateral, oro- and hypopharynx as well as floor of mouth and palate.

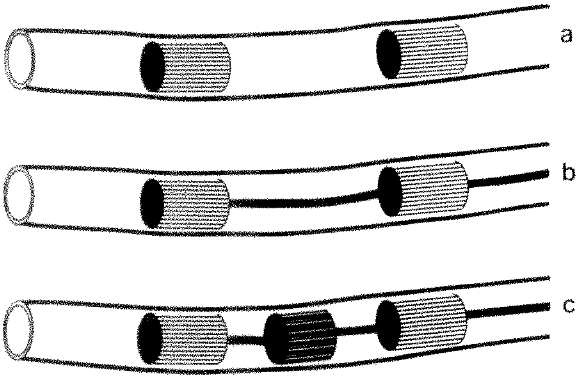


FIG. 3.

Sources in nylon ribbon. Note fine wires and marker used with inactive (dummy) sources to aid in identification of individual ribbons: (a) dummy sources or live sources in nylon ribbon; (b) properly spaced dummy sources with fine wire between all sources; (c) normally spaced dummy sources with identification marker and wire between sources.

this time, changes in temporal loading of specific ribbons to complement the already fixed geometrical constraints are determined. In this way differential loading (or unloading) can sometimes be used to ensure that the whole tumour volume receives a "tumouricidal" dose. The anoxic centre often receives a somewhat higher dose than the periphery. Maximum and minimum doses at selected points in the previously outlined volume of interest are recorded. The minimum dose at the edge of the tumour volume usually determines the implant time. These isodose overlays are ready for review an hour to an hour and a half after the localization radiographs are taken, and often before the actual loading with radioactive sources. This permits a degree of flexibility that is not possible when active sources are implanted directly.

The dose calculation system relies heavily on good localization films and on the availability of a computer with a graphic digitizing input device. The calculation algorithm requires that each source be located and identified on each film. Special inactive (dummy) source ribbons were developed for rapid identification of the sources, one ribbon at a time. The dummy ribbon contains a fine wire which can be seen linking the individual dummy seeds in the radiographs (Fig. 3). In addition, in each ribbon there is a ribbon identification marker. This marker is smaller than the dummy sources and is placed randomly between different pairs of seeds in each ribbon. These markers and the connecting wires make it easier to identify the individual ribbons and follow them through the implant. The ability to identify the ribbons expeditiously, and a digitizer to enter automatically the locations of individual seeds into the computer, are essential if the calculations of dose distribution are to be completed promptly. This information must be available in sufficient time to affect decisions regarding the implant either before or shortly after it is loaded with active sources.

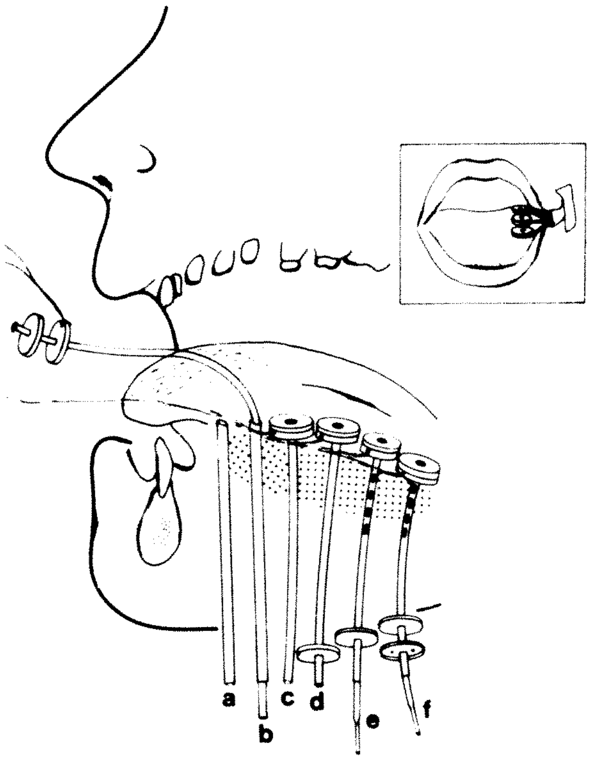


Fig. 4.

(Inset) Grouping of silk threads in Penrose drain; (a) insertion of hollow needle; (b) threading of plastic tube with gold and plastic buttons attached; (c) removal of hollow needle; (d) fixation of plastic tube by gold and second plastic button; (e) placement of inactive sources for radiographs; (f) placement and fixation of active sources.

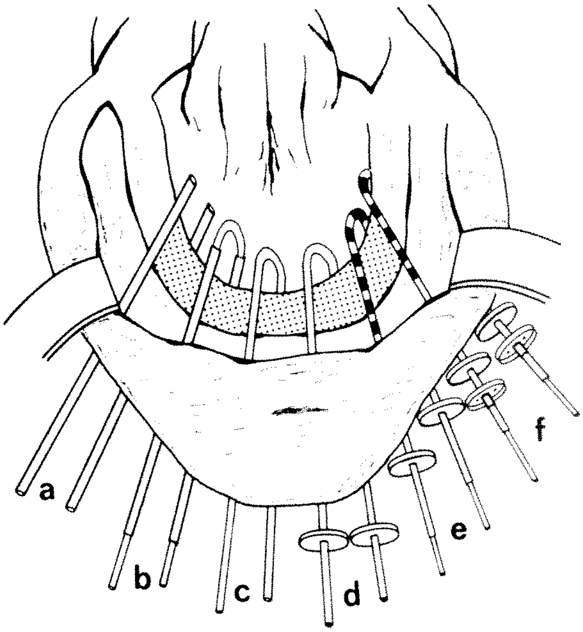


Fig. 5.

(a) Insertion of pair of needles; (b) threading of plastic tube; (c) removal of hollow needles; (d) fixation of plastic tube by plastic buttons; (e) placement of inactive sources for radiographs; (f) placement and fixation of active sources.

Removal

(a) A special wire-cutter is employed; it is adjusted to clip only the outer plastic tube and to spare the active source ribbons. The plastic tube is cut between the plastic and the steel button, revealing the active source ribbon.

(b) The active source ribbon is removed and placed in an appropriate protective container.

(c) The extruding plastic tube is then cut off close to the skin and the remaining portion is pulled out. *Caution:* The active source ribbon is always removed first. Failure to do so may result in leaving it behind when the plastic tube is removed.

(The plastic tube and button technique is useful for lesions of the lip and neck.)

Gold button technique

This is shown in Fig. 4 (Syed *et al.*, 1975).

1. Hollow steel needles of 17 gauge are inserted through the neck throughout the volume of interest in the oral cavity. (One end of the needle projects through the mucosal surface, the other presents on the skin.)
2. Plastic tubes, with both a gold and a plastic button attached to the already sealed intra-oral end (and a silk thread tied to the plastic button), are threaded through the needles, starting at the intra-oral end of the needle. (The plastic button is used as a separator to keep the sealed end away from the surface and thus permits the source to protrude slightly beyond the surface.)
3. As the hollow steel needles are removed, the plastic tubes are left in their place.
4. In order to fix these plastic tubes in place, snugly-fitting plastic buttons are pushed onto the tubes relatively close to the skin. When all the tubes are fixed in place, the group of silk threads is brought through a ¼ in. (6 mm) Penrose drain, which is taped to the cheek (see inset in Fig. 4).

The localization, computerized calculation of isodose distributions, and the loading procedures are essentially the same as those described above. The gold buttons serve a dual role: to space and retain the plastic tubes *in situ*, and to protect overlying tissues against unnecessary irradiation and trauma. (The gold button technique is useful for oral and oropharyngeal carcinomas.)

Loop technique

This is shown in Fig. 5.

1. Pairs of hollow steel needles of 17 gauge are inserted through the neck on either side of the mandible throughout the volume of interest.
2. Both ends of each plastic tube are then threaded through a pair of steel needles so that the resulting inverted "U" is wrapped over the alveolar ridge.
3. The steel needles are removed and the plastic tubes are left in their place.

(The loop technique is used primarily when cancers encroach upon the mandible.)

RESULTS

From February 1, 1974 to October 1, 1975, 64 patients with persistent or "recurrent" cancers of the head and neck after initial treatment by irradiation to "full tolerance" levels, with or without surgery, were treated for palliation or possible salvage at the LAC-USC Medical Center and the Southern California Cancer Center (Table I). Local persistence was identified at least four months after the completion of the initial treatment. All 64 patients had received about 6000 rad at the initial treatment and in 12 surgery had been performed in addition.

The results of retreatment with ^{192}Ir are given in Table II. The doses delivered ranged from 4500 to 6000 rad in three to five days. Our follow-up period, averaging only 24 months (18 to 36 months), is too short for a statistically significant evaluation of survival. At the time of writing, 28 of our 64 patients (44%) were alive with local control and at least good

TABLE II

RESULTS OF RETREATMENT OF HEAD AND NECK CANCER BY AFTERLOADING ^{192}IR IMPLANT

Site	No. of patients	Interstitial retreatment dose (rad)	Complete tumour regression		Partial tumour regression		Alive 18 months without disease	Deaths*
			Without necrosis	With necrosis	Without necrosis	With necrosis		
Floor of mouth	7	5000–6000	2	2	1	1	4	3
Mobile tongue	6	4500–5000	2	1	0	2	3	3
Retromolar area	9	5000–6000	3	1	1	2	4	5
Base of tongue and vallecula	10	4500–6000	3	2	1	2	5	5
Soft palate and uvula	4	5000–6000	4	0	0	0	3	1
Lip	1	5000	1	0	0	0	1	0
Gum, alveolar ridge	1	5500	0	1	0	0	0	1
Buccal mucosa	2	5500–6000	1	0	1	0	1	1
Posterior pharynx	2	5000	2	0	0	0	1	1
Antrum	1	5000	0	0	0	1	0	1
Neck masses	21	5000–6000	5	1	7	3	6	15
	64		23	8	11	11	28 (44%)	36 (56%)

*No tumour regression had occurred in 11 of these 36 patients.

TABLE III

PATTERNS OF FAILURE (DEATHS*) AFTER RETREATMENT OF HEAD AND NECK CANCERS BY AFTERLOADING IRIDIUM IMPLANT

Site	Death with local failure		Death associated with metastatic disease	Death from intercurrent disease	Total deaths
	With necrosis	Without necrosis			
Floor of mouth	1	2	0	0	3
Mobile tongue	2	1	0	0	3
Retromolar area	2	3	0	0	5
Base of tongue and vallecula	2	3	0	0	5
Soft palate and uvula	0	0	0	1	1
Gum, alveolar ridge	0	0	1	0	1
Buccal mucosa	0	1	0	0	1
Post pharynx	0	1	0	0	1
Antrum	1	0	0	0	1
Neck masses	3	6	6	0	15
	11 (17%)	17 (26%)	7 (11%)	1 (2%)	36 (56%)

*Of 64 patients retreated 36 (56%) have died to date and 28 (44%) are alive with a satisfactory response.

palliation. "Local control" means total tumour regression maintained clinically throughout the follow-up period of 18 to 36 months. "Good palliation" means relief of pain, bleeding and dysphagia associated with total tumour regression and no evidence of necrosis. Thirty-six of the 64 (56%) have died. Of these, two had no detectable tumour at the site of implant at the time of death but in 11 there had been no sign of tumour regression after retreatment.

Four of the 12 patients who had had surgery in addition to irradiation as the initial treatment were alive without disease and eight were dead. Twenty-four of the 52 patients who had had irradiation only as the initial treatment were alive without disease, and 28 were dead.

Nineteen of the 64 patients (30%) developed necrosis in the implant area. Six of these 19 went on to develop orocutaneous fistulas and five of these died. The one patient with fistula who was alive has survived three years without evidence of cancer. He received treatment by hyperbaric oxygen and was ready for reconstructive surgery. Seven of the 13 who developed necrosis without fistulas were alive without evidence of cancer and were responding slowly to conservative management.

Deaths have occurred in 36 of the 64 retreated patients (28 with local failure, seven associated with distant metastatic disease, and one as a result of intercurrent disease). Table III shows the patterns of failure.

Discussion

The 64 patients reported here were mostly candidates for palliative management. They had all been irradiated previously to "full tolerance" levels (about 6000 rad), and 12 had had surgery in addition. Almost all were in bad general condition. For the most part, they were unsuitable for an attempt at surgical salvage because of the site or the extent of the involvement. Prognosis was poor in all. In this group, our primary aim was to obtain good palliation, by controlling the local disease at least temporarily, while keeping morbidity at a minimum.

Under the circumstances, the number of relatively long-term local controls (44% for 18 months or more) has proven quite gratifying. If we accept the statement of Pierquin *et al.* (1970) that "local control of primary tumour six months after endoradiotherapy with ^{192}Ir is tantamount to local cure", we could anticipate an occasional long-term survival in these otherwise hopeless cases. Our follow-up period of 18–36 months (averaging 24 months) is too short, however, for statistically significant evaluation of survival.

The complication rate of 30% is quite high, but we consider this acceptable in view of the poor prognosis of the patients involved.

We have been unable to locate reports in the literature on the results of *retreatment* in head and neck cancer with afterloading interstitial ^{192}Ir implants. To date our results with this modality seem to compare favourably with results cited by other authors for retreatment by surgery, by irradiation and by chemotherapy.

Oncologists are aware that management of persistent or "recurrent" head and neck cancer is rarely satisfactory. Fletcher (1974) points out that "... *radiation* for post-radiation recurrences following a full dosage is contraindicated since it will almost invariably cause necrosis and failure to control the disease. A satisfactory result is not feasible ...".

Gelinas and Fletcher (1973) reporting on the results of *surgical* salvage in 106 failures (out of 554 patients irradiated for carcinomas of faucial arch, tonsillar fossa and base of tongue from 1954 to 1967) cited only 34 "successful cases". Thus 72/106 (68%) remained as unsalvaged "ultimate failures".

Votava *et al.* (1972) reported on 75 patients with advanced cervical lymph node metastases. Of 35 patients with primary control, the neck was uncontrolled by irradiation in 17. Of the 17 failures, two were salvaged by surgery. There were 15 "ultimate neck failures" in the 35 patients with primary control.

Williams (1974) reported on the results of radical surgery for the retreatment of 67 recurrences in 144 patients with head and neck cancers which had been treated initially by surgery; he cited a 16% crude five-year survival rate. He did not discuss the palliative status of the 84% who failed.

Sealey and Hellman (1972) reported on the treatment by multiple agent intra-arterial infusion of 39 patients who had persistent disease *after irradiation*; they stated ... "we were uniformly unsuccessful in obtaining a response ...". (Or course, response was considerably better in their extensive but previously untreated head and neck cancer cases.) Whereas complication rates in two previously untreated groups were only 30% and 26%, the complication rate in the 39 patients who had persistent disease after irradiation was 65%.

Oberfield *et al.* (1973) reported on regional arterial chemotherapy with multiple agents in 46 patients with advanced oropharyngeal tumours after surgical excision and local irradiation; they cited 33% alive for more than one year. But only 8% maintained complete tumour regression for that year.

Dowell *et al.* (1975) summarized the results of six different systemic multiple drug protocols pursued under Central Oncology Group auspices for advanced head and neck malignancies. (Of the 158 patients involved, 67% had had prior radiotherapy, but results were not catalogued according to this criterion.) They concluded however, that . . . "advanced head and neck cancer remains a difficult disease to palliate by any modality . . .". The response rate of 50% of squamous cell tumours treated with the five-drug (systemic) protocol compared favourably with several reported series of patients treated by regional infusion techniques, but in the four- and five-drug protocol the incidence of "severe to life-threatening thrombopenia" was 12%.

The case material reported here is limited to patients quite similar to those relatively hopeless cases cited above. Our 64 patients were referred to us with "unresectable" persistent disease at least four months after unsuccessful treatment by presumably definitive irradiation (plus more or less definitive surgery in some patients). As of May 1, 1977, after our average follow-up period of 24 months, 44% of these presumably hopeless patients still have local control with at least good palliation maintained for 18 to 36 months. An additional 34% have had 50% tumour regression. Thus a total of 83% have had some satisfactory response to retreatment. Our experience to date leads us to believe that local tissue tolerance to retreatment by this afterloading interstitial ^{192}Ir technique is considerably better than that which would be anticipated for retreatment using external irradiation alone. This interstitial modality offers a worthwhile alternative form of management for persistent carcinomas of the head and neck.

REFERENCES

AXTELL, L. M., CUTLER, S. J., and MYERS, M. H., 1972. End results in cancer. *Report No. 4, National Cancer Institute, Bethesda, Md. Publication number (NIH) 73–272, Vol. 4.*

DOWELL, K. E., ARMSTRONG, D. M., AUST, J. B., and CRUZ, A. B., JR., 1975. Systemic chemotherapy of advanced head and neck malignancies. *Cancer, 35*, 1116–1120.

FLETCHER, G. H., 1974. *Textbook of Radiotherapy*, 2nd edn, pp.215 (Lea and Febiger, Philadelhpia).

GELINAS, M., and FLETCHER, G. H., 1973. Incidence and causes of local failure of irradiation in squamous cell carcinoma of the faucial arch, tonsillar fossa, and base of the tongue. *Diagnostic Radiology, 18*, 383–387.

MEREDITH, W. J., GREEN, D., and KAWASHIMA, K., 1966. The attenuation and scattering in a phantom of gamma rays from some radionuclides used in mould and interstitial gamma-ray therapy. *British Journal of Radiology, 39*, 280–286.

MOHAN, R., 1975. Memorial dose distribution computation service—brachy interstitial and intracavitary dose computation program users guide (Memorial Hospital, New York).

OBERFIELD, R. A., CZDY, B., and BOOTH, J. C., 1973. Regional arterial chemotherapy for advanced carcinoma of the head and neck: a ten-year review. *Cancer, 32*, 82–88.

PIERQUIN, B., CHASSAGNE, D. M., and COX, J. D., 1970. Towards consistent local control of certain malignant tumors. *Radiology, 99*, 661–667.

SEALEY, R., and HELLMAN, P., 1972. Treatment of head and neck cancer with intra-arterial cytotoxic drugs and radiotherapy. *Cancer, 30*, 187–189.

SYED, A. M. N., FEDER, B. H., GEORGE, F. W., SCHAEFLEIN, J. W., and NEBLETT, D. L., 1975. Management of extensive residual cancer with interstitial iridium implant: a preliminary report. In *Afterloading: 20 years of experience, 1954–1975*, Basil S. Hilaris, pp. 119–124 (Memorial Sloan-Kettering Cancer Center, N.Y.).

VOTAVA, C., FLETCHER, G., JESSE, R. H., and LINDBERG, R. D., 1972. Management of cervical nodes either fixed or bilateral, from squamous cell carcinoma of the oral cavity and faucial arch. *Therapeutic Radiology, 105*, 417–420.

WILLIAMS, R. C., 1974. Recurrent head and neck cancer: the results of treatment. *British Journal of Surgery, 61*, 691–697.

Book review

Atlas of Cardiovascular Nuclear Medicine. By H. W. Strauss, B. Pitt, J. Rouleau, I. K. Bailey and H. N. Wagner, pp. xiii+194, 665 illus, 1977 (The C. V. Mosby Company, St. Louis; Distributed in UK by Henry Kimpton, London). £35·70.

This atlas in no way pretends to be a comprehensive collection of radionuclide cardiology, and its contents are limited to a consideration of radioactive thallium myocardial perfusion studies, ^{99}Tc^{m} technetium pyrophosphate myocardial infarct imaging and the use of the equilibrium electrocardiographically gated blood pool technique. The majority of the book consists of case histories where two or more of the methods have been used. Although these are instructive in themselves, they are set in too unsubstantial a framework to be considered authoritative.

The crucial relationship between thallium images and the distribution of coronary vascular anatomy is limited to only one page of description, and the lack of complementary angiographic data accompanying the case histories is a major weakness of the book. There is no indication of the relative frequency with which a particular image defect is associated with a particular arterial abnormality, and consequently there is not much discussion on the reliability of any particular interpretation.

The illustrations that form the major strength of the book are adequate, and the accompanying grey tone diagrams are useful. It is not particularly easy to match a given perfusion image in one's hand with an illustration in the book, but familiarity with the book undoubtedly improves one's nuclear cardiological faculties.

It is certainly the best attempt to date to create a representative atlas of cardiovascular nuclear medicine.

K. E. BRITTON.

1978, *British Journal of Radiology*, *51*, 821–822 OCTOBER 1978

Technical notes

Positioning errors in bone mineral measurement

By M. I. Al Jarallah, B.Sc., Ph.D.,* J. A. Archer-Hall, M.A., B.Sc., M.R.C.S., L.R.C.P. and P. E. Francois, B.Sc., Ph.D., F.Inst.P.

Physics Department, University of Aston, Birmingham B4 7ET

(*Received April, 1978*)

Several techniques have been described for estimating bone mineral by observing the transmission of X rays or low energy γ rays through parts of the skeleton. Frequently these measurements are made by scanning the ulna a few centimetres from the distal end. This type of observation is particularly useful for serial studies to observe the progress of disease or therapy. The dimensions of the bone at its distal end vary with position, as noted by Horsman and Leach (1974). It is therefore important to reposition the arm accurately, in respect to both longitudinal position and rotation, to ensure that the bone is scanned similarly each time.

By making observations on a number of ulnas obtained post-mortem we have measured the magnitude of errors likely to be caused by failure to reposition accurately.

EXPERIMENTAL

Pieces of five ulnas were obtained post-mortem and were scanned using a narrow bean of polychromatic X rays by the method used by Archer-Hall *et al.* (1973). In this technique a step wedge of an artificial bone-like material is placed alongside the bone to serve as a standard. A typical scan is shown in Fig. 1. Various measurements made on the scan may be used as parameters to indicate the bone status. We have considered the measurement of the peak heights (marked h_1 and h_2 on the scan) which correspond to the greatest path lengths through the cortex, and the measurement of the total area of the scan which after correction for non-linearity of the scale gives a measurement of the total mineral content of the section of bone scanned.

The pieces of bone, each about 15 cm long, were fixed in jigs so that they could be scanned at the normal position about 3 cm from the ulna styloid, and a few millimetres either side of this. Similar repeat measurements were made with the bone rotated through angles of up to 10° from the normal supinated position such as might readily occur in practice with a patient. Typical results are shown in Figs. 2–4 in which differences between the measurements made on the scans and those made on the scan taken at the standard scanning position are expressed as percentages of the latter.

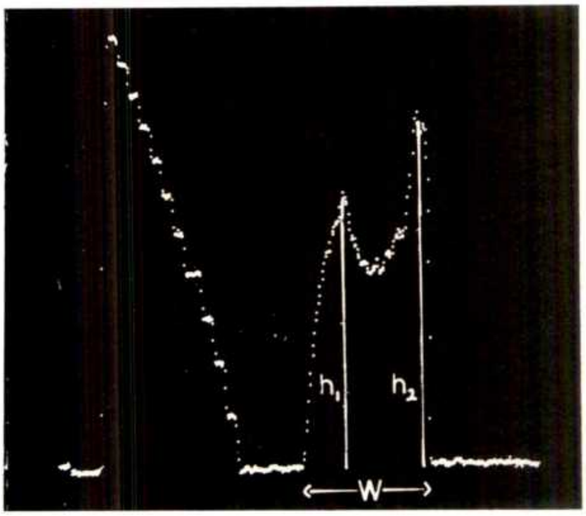


FIG. 1.

A typical scan of ulna and step wedge. The peak heights h_1, h_2 correspond to the maximum path lengths through the cortex. W measures the width of the bone.

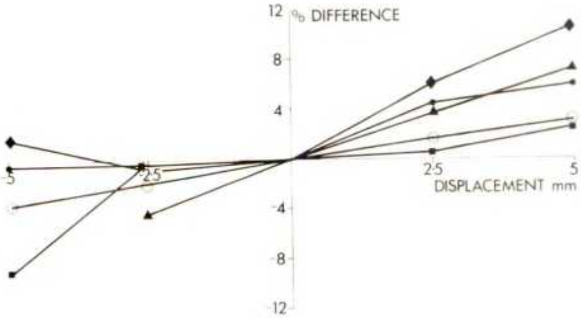


FIG. 2.

The variation of scan area with displacement. The different symbols refer to the five ulnas.

---

*Present address: Department of Physics, College of Sciences, University of Petroleum and Minerals, Dhahran, Saudi Arabia.

1978, *British Journal of Radiology*, *51*, 822–823

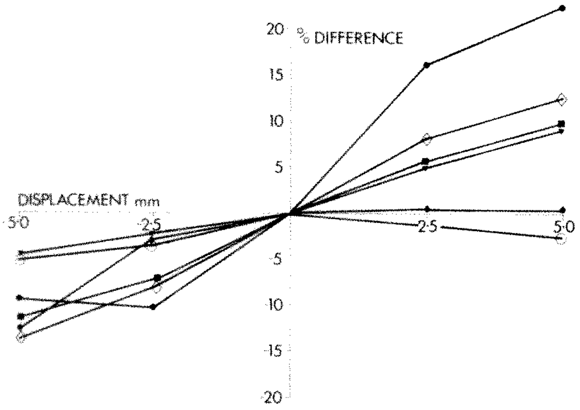


FIG. 3.

The variation of peak heights with displacement.

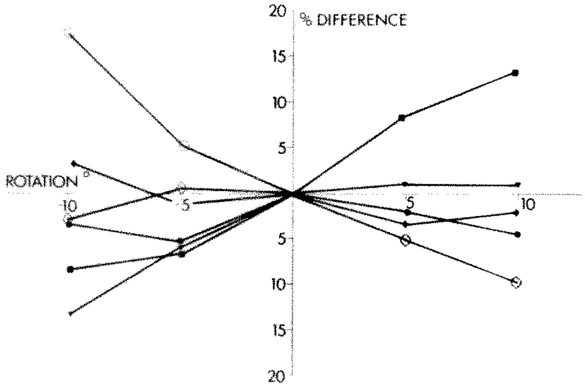


FIG. 4.

The variation of peak heights with rotation.

Figure 2 shows the changes in scan area with movements of up to 5 mm either side of the standard scanning position. As would be expected the scan area usually increases with displacement towards the elbow and decreases with movement towards the distal end of the bone. The maximum change is about 10% for a 5 mm movement and the average is about 5%. Therefore an error in the scan area of the order of 1% per mm may result from inaccurate longitudinal repositioning. This is similar to the result found by Sorenson and Cameron (1968) in measurements made on the radius. The width W was found to change very little with this movement. The variations of scan area with rotations of up to 10° either side of the normal position were all within 2% which is the maximum expected experimental uncertainty of the area measurements. This is to be expected since the scan area measures the total mineral in the section scanned.

Figure 3 shows the variation in the peak heights with linear displacement of the bone. Again the peak heights increase with distance from the ulna styloid. The average variation of peak height is about 2% per mm. The variation of peak heights with rotation of the bone is shown in Fig.4. No clear pattern is apparent, indicating that the cross sectional shape of the bone is very different from one specimen to another. Nevertheless, for individual bones considerable variation is possible, changes of over 1% per degree having been observed.

ACKNOWLEDGMENT

We should like to thank Dr. P. B. Carpenter of the Radiology Department, Dudley Road Hospital for his help.

REFERENCES

ARCHER-HALL, J. A., CARPENTER, P. B., EDWARDS, J. P. N., and FRANCOIS, P. E., 1973. A new method of bone mineral estimation using a conventional X-ray set. *British Journal of Radiology*, *46*, 375–380.

HORSMAN, A., and LEACH, A. E., 1974. The estimation of the cross-sectional area of the ulna and radius. *American Journal of Physical Anthropology*, *40*, 173–185.

SORENSON, J. A. and CAMERON, J. R., 1968, Measurement of bone mineral by direct photon absorption, Progress Report COO–1422–22 (University of Wisconsin).

"Floppy" into "flippy" – or two for the price of one

By L. G. Brock, B.Sc. F.R.C.S., D.M.R.D.

Neuroradiology Department, Walton Hospital, Liverpool and Associated Department of Neurological Sciences, University of Liverpool

(*Received March, 1978*)

The floppy discs supplied for rapid-access storage of data obtained from the EMI brain scanner hold data from eight slices, and cost approximately £4. As Cromwell *et al.* (1977) have shown, the cost per slice can be halved by the simple manoeuvre of punching two holes in the plastic cover of the disc. The floppy disc is thus transformed into a flippy disc which will hold data from 16 slices, eight per side, with no obvious quality deterioration or print-through. Apart from reduction in capital cost, other obvious benefits are more compact storage, and diminished disc handling for a given work load. It

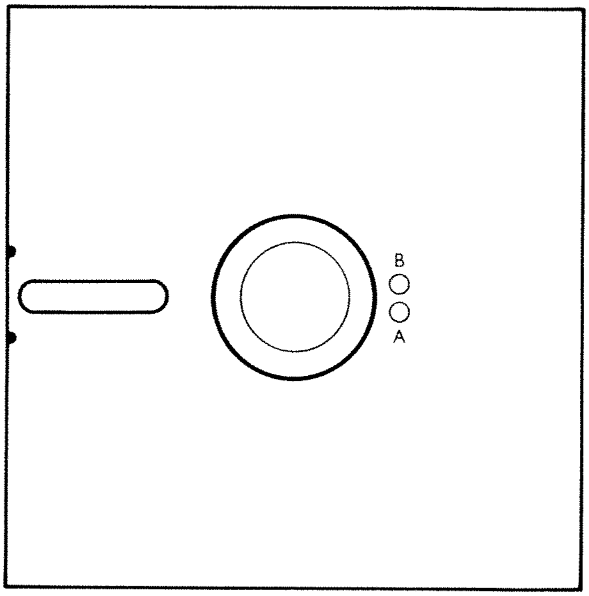


FIG. 1.

seems worthwhile to give details of methods of making the holes, and of suitable equipment which is readily available at low cost, as this aspect was not fully covered in the original communication (Fig. 1).

The hole "A" is present in the disc cover as supplied by EMI, and if the disc is viewed en-face, in the position in which it is inserted into the slot of viewing unit, "A" is seen to be centred approximately 5 mm below the horizontal mid-line. The new hole "B" should be punched at a similar distance from the horizontal mid-line, but above it and in line with the original hole. The reverse side of the disc cover should be treated similarly, but here the original hole is above the horizontal mid-line, and the new hole must be correspondingly below the mid-line.

The disc will, after punching, be accepted by the viewing unit in both normal and reversed positions. Erasing, formating, picture transfer and viewing, all take place after reversal of the disc, exactly as if a second (unmodified) disc were being used.

The original hole ("A") is approximately 7.5 mm diameter. It is not easy to obtain a 7.5 mm punch, but 6 mm punches are readily available and this size of hole seems perfectly adequate to transmit a beam of light which passes through a small hole in the magnetic disc itself to operate a sensing device in the drive unit.

I find a Velos 4362 single hole punch satisfactory. It costs approximately £5 and can be bought from commercial stationers. Cheaper punches such as those used for leather work do not cut cleanly through the fleecy lining of the disc cover without frequent time-consuming sharpening. Puncturing the holes requires some care, but is not particularly exacting. Until the operator has had some practice it is advisable to mark the horizontal midline as a guide, but it soon becomes possible to judge the correct position by eye. I find it helpful to slip a strip of smooth cardboard (about 4 or 5 cms wide) through the centre of the hole of the cover between it and the disc, under the site of the proposed hole. The delicate magnetic disc is then protected, and the disc cover can be lifted sufficiently to allow the lower jaw of the punch (which has a shape rather like a pair of pliers) to slide under the cover, along the cardboard strip. The waste portion should not be allowed to escape inside the disc cover. One way of preventing this is to place a strip of adhesive cellulose tape over the exit hole in the punch, and several pieces can accumulate before the channel need be cleared.

Since the purpose of the holes is to transmit a light beam, there is an obvious simplification: manoeuvre the magnetic disc into a suitable position and then punch a hole through both layers of the cover with the magnetic disc between. Unfortunately this method does not work. Other simplifications are under investigation. I understand that discs, ready punched for two sided operation can be obtained from alternative suppliers for less than £3, but have not yet been able to test them. Many departments will have large stocks of single sided discs, and punching remains a relatively easy way of making worthwhile economies.

REFERENCE

CROMWELL, L. D., MOORE, W. E., SCHUMACHER, D., and SALAM, A., 1977. A method of reducing cost in CT systems that employ floppy discs. *American Journal of Roentgenology*, *129*, 1123–1124.

1978, *British Journal of Radiology*, *51*, 824

Technical notes

New grey tone rapid process films for ultrasound imaging

By W. A. Copland, V.R.D., M.B., Ch.B., F.R.C.S.E., F.R.C.R., and S. R. Wild, M.B., Ch.B., F.R.C.R.

Department of Radiology, Western General Hospital, Edinburgh EH4 2XU

and W. N. McDicken, B.Sc., Ph.D.

Department of Medical Physics and Medical Engineering, Western General Hospital, Edinburgh EH4 2XU

(*Received March, 1978*)

Multiformat camera-back X-ray film holders, and automatic format systems are increasingly popular in X-ray departments with ultrasound facilities because of the ease of processing, labelling and handling X-ray type film together with the relatively low cost by comparison with Polaroid film.

In a previous communication by Niemen *et al.* (1976) comparisons were made of various rapid process films for recording grey scale ultrasound from black and white television monitors. Kodak RP/SU (subtraction) film was considered most suitable as regards tonal range, speed and latitude. The same technique has now been applied to new X-ray type rapid process film introduced specifically for grey scale imaging.

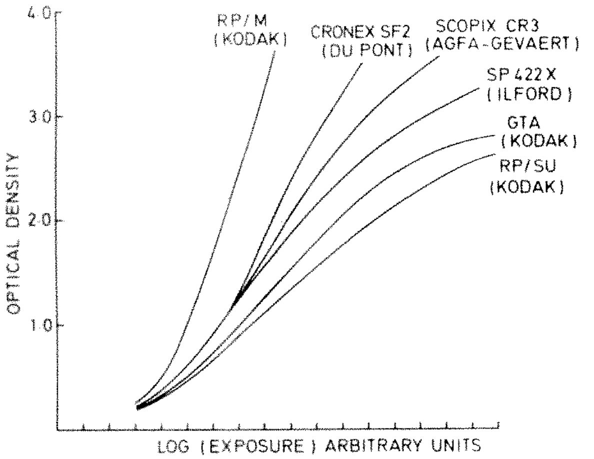


Fig. 1.

Characteristic response curves for new grey tone X-ray type film. Relative film speeds have been ignored for ease of comparison of film gammas.

Optical film densities obtained with a standard light source and an optical step wedge have been plotted against the logarithm of the exposure. The results reproduced in graph form (Fig. 1) show that while Kodak RP/SU still has the lowest gamma (gradient), all the new emulsions examined are suitable for recording grey scale images. Subjective evaluation of clinical material revealed a preference for films of a slightly higher gamma than RP/SU. The new emulsions cover the acceptable range of film gamma while retaining suitable latitude for routine use.

The graphical results of this project have confirmed the subjective assessment of the films' characteristics. While the final choice of product remains an individual preference, these results provide a basis for selection.

Grateful acknowledgment is made to those manufacturers who supplied film for evaluation. Not all the products examined may be available commercially at the time of publication.

REFERENCE

Niemen, M., McDicken, W. N., and Copland, W. A., 1976. Ultrasonic grey scale recording with rapid processing film. *British Journal of Radiology*, *49*, 895.

1978, *British Journal of Radiology*, *51*, 825–826 OCTOBER 1978

Case reports

Diagnosis of an ileal duplication with sodium pertechnetate ^{99}Tc^{m}

By N. W. Garvie, M.A., M.R.C.P., G. S. M. Harrison, M.A., F.R.C.S. and
D. M. Ackery, M.A., M.B., M.Sc.

Wessex Regional Department of Nuclear Medicine, and Wessex Paediatric Surgical Centre, Southampton General Hospital

(*Received December, 1977*)

Massive rectal haemorrhage is an alarming symptom at any age, but particularly in an infant, and will often require surgical intervention. Localization of the bleeding source prior to surgery is preferable to performing a "blind" laparotomy. The most common cause of this problem in infancy is peptic ulceration associated with ectopic gastric mucosa in either a Meckel's diverticulum or an enteric duplication (Jones, 1976). ^{99}Tc^{m} pertechnetate scanning has successfully detected the more common Meckel's diverticulum pre-operatively (Jewett, *et al.*, 1970). We have demonstrated a duplication of the terminal ileum presenting with rectal bleeding by this technique.

CASE HISTORY

A ten month old male infant was transferred to the Wessex Paediatric Surgical Centre with severe anaemia and a six week history of intermittent painless rectal bleeding. A barium enema showed no abnormality in the colon, but failed to fill the terminal ileum. A ^{99}Tc^{m} pertechnetate abdominal scan demonstrated an area of increased activity in the right iliac fossa (Fig. 1).

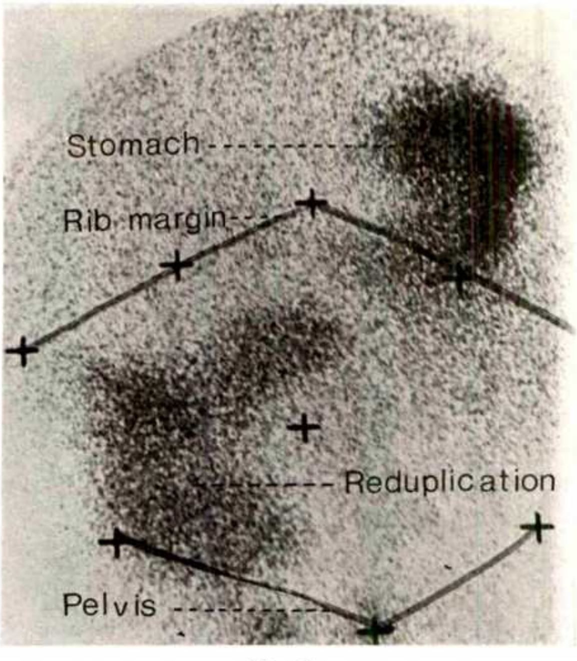


FIG. 1.
Pertechnetate abdominal image showing uptake in reduplication and normal stomach.

At laparotomy a 20 cm duplication of the terminal ileum was resected (Fig. 2). The surface of the ileum was irregular with focal haemorrhages. Histology showed normal mucosa in the ileum but the duplication was lined entirely by gastric mucosa. The post-operative course was uneventful.

DISCUSSION

Small bowel duplication cysts are uncommon, and are probably caused by the persistence of neuroenteric communications. Ileal duplications account for approximately 30% of all enteric duplications, and commonly present in the first year of life as an abdominal mass with symptoms of intestinal obstruction (Grosfield *et al.*, 1970). Communications between the duplication and the ileum may exist, but are often narrow and conventional barium contrast examinations frequently are unsuccessful.

Up to 50% of ileal duplications contain ectopic gastric mucosa, and in these patients peptic ulceration leading to peritonitis or massive rectal haemorrhage may occur (Basu *et al.*, 1960). This group can be identified by sodium pertechnetate abdominal scanning, which is a recognized technique for the

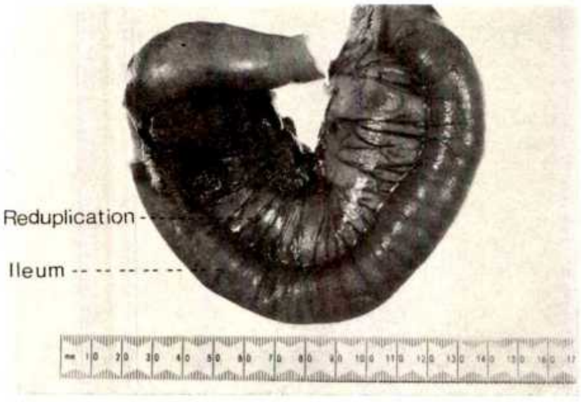


FIG. 2.
Operative specimen showing reduplication segment of ileum.

1978, *British Journal of Radiology*, *51*, 826–828

localization of ectopic gastric mucosa in Meckel's diverticulum (Berquist *et al.*, 1976), Barrett's oesophagitis (Berquist *et al.*, 1973) and colonic duplications (Wilson *et al.*, 1977). Two previous ileal duplications, both presenting with rectal bleeding, have been detected by this method (Schwesinger *et al.*, 1975; Winter, 1977) and we believe that this records the first example in the United Kingdom.

Sodium $^{99}\text{Tc}^{m}$ pertechnetate abdominal scanning is essentially non-invasive and causes little discomfort to the patient. The radiation dose is similar to that incurred from fluoroscopy during gastrointestinal radiography (Webster *et al.*, 1974). We believe that it is a valuable technique in the preoperative assessment of the infant with rectal bleeding.

REFERENCES

BASU, R., ROBSHALL, I., and RICKHAM, P. P., 1960. Duplications of the alimentary tract. *British Journal of Surgery*, *47*, 477–484.

BERQUIST, T. H., NOLAN, N. G., STEPHENS, D. H., and CARLSON, H. C., 1976. Specificity of $^{99}\text{Tc}^{m}$ pertechnetate in the scintigraphic diagnosis of Meckel's diverticulum: review of 100 cases. *Journal of Nuclear Medicine*, *17*, 465–469.

BERQUIST, T. H., NOLAN, N. G., CARLSON, H. C., and STEPHENS, D. H., 1973. Diagnosis of Barrett's oesophagitis by pertechnetate scintigraphy. *Mayo Clinic Proceedings*, *48*, 276–280.

GROSFIELD, J. L., O'NEILL, J. A., and CHATWORTHY, H. W., 1970. Enteric duplications in infancy and childhood. An 18 year review. *Annals of Surgery*, 172, 83–90.

JEWETT, T. C., DUSZYNSKI, D. O., and ALLEN, J. E., 1970. The visualisation of Meckel's diverticulum with $^{99}\text{Tc}^{m}$ pertechnetate. *Surgery*, *68*, 567–570.

JONES, P. G., 1976. *Clinical Paediatric Surgery, 2nd edn.* (Blackwell Scientific Publications).

SCHWESINGER, W. H., CROOM, R. D., and HABIBIAN, M. R., 1975. Diagnosis of an enteric duplication with pertechnetate $^{99}\text{Tc}^{m}$ scanning. *Annals of Surgery*, *181*, 428–430.

WEBSTER, E. W., ALPERT, M. N., and BROWNELL, G. L., 1974. Radiation doses in paediatric nuclear medicine and diagnostic X-ray procedures. *Paediatric Nuclear Medicine*, pp. 34–58 (W. B. Saunders and Co., Philadelphia).

WILSON, J. P., WENZEL, W. W., and CAMPBELL, J. B., 1977. Technetium scans in the detection of gastrointestinal haemorrhage. *Journal of the American Medical Association*, *237*, 265–266.

WINTER, P. F., 1977. Diagnosis of an ileal duplication cyst. *Journal of the American Medical Association*, *237*, 1352–1353.

Chronic oesophageal stricture due to moniliasis

By F. M. Kelvin, M.B., M.R.C.P.(U.K.), F.R.C.R., W. M. Clark, M.D., W. M. Thompson, M.D.*
and T. Hauch, M.D.

Departments of Radiology and Medicine, Duke University Medical Center, Durham, North Carolina, 27710, U.S.A.

(*Received March, 1978*)

Treatment of oesophageal moniliasis with nystatin and amphotericin B usually results in rapid recovery. A case is presented in which, despite complete relief of symptoms after anti-monilial therapy, a permanent stricture developed necessitating placement of a feeding gastrostomy. Athey *et al.* (1977) observed one stricture in 17 patients with oesophageal moniliasis confirmed by culture, suggesting this to be a rare complication.

CASE HISTORY

A 17-year-old male was found to have acute myelogenous leukaemia. Haematological evaluation revealed a haemoglobin of 7.9 g%, a platelet count of 45 000/mm^3 and a white blood cell count of 9400/mm^3 with 90% blast cells. A bone marrow aspirate yielded 90% immature myeloid blast cells.

He was treated with two courses of cytosine arabinoside and daunorubicin hydrochloride. During the first course he developed fever and dysphagia. A double contrast barium swallow showed evidence of monilial oesophagitis (Fig. 1). Monilia was cultured from the oropharynx. An eight-day course of amphotericin B and nystatin produced complete symptomatic relief. The patient was discharged from the hospital in haematologic remission. One month after discharge he again developed dysphagia and a barium swallow demonstrated a long stricture involving the middle third of the oesophagus (Fig. 2). Oesophagoscopy confirmed the presence of a tight oesophageal stricture which could not be dilated. Because the patient was having severe dysphagia and had lost a great deal of weight, a gastrostomy feeding tube was placed.

Six weeks later a barium swallow demonstrated that the oesophageal stricture was unchanged (Fig. 3).

DISCUSSION

Oesophageal moniliasis has become increasingly common since the advent of more successful chemotherapy for malignant disease. This is especially true of leukaemic patients. The diagnosis should be suspected when such a patient complains of acute odynophagia or dysphagia. In severely ill patients a

---

*Picker Scholar, James Picker Foundation.

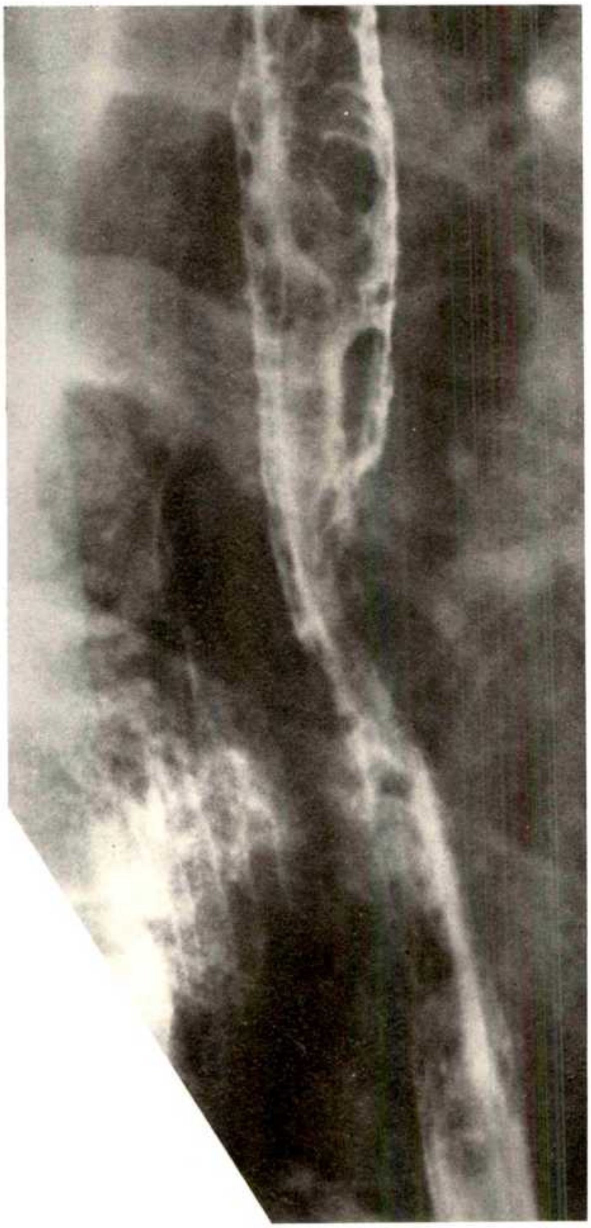


FIG. 1.

Double contrast barium swallow shows irregular outline and multiple filling defects in upper two-thirds of oesophagus consistent with acute moniliasis.

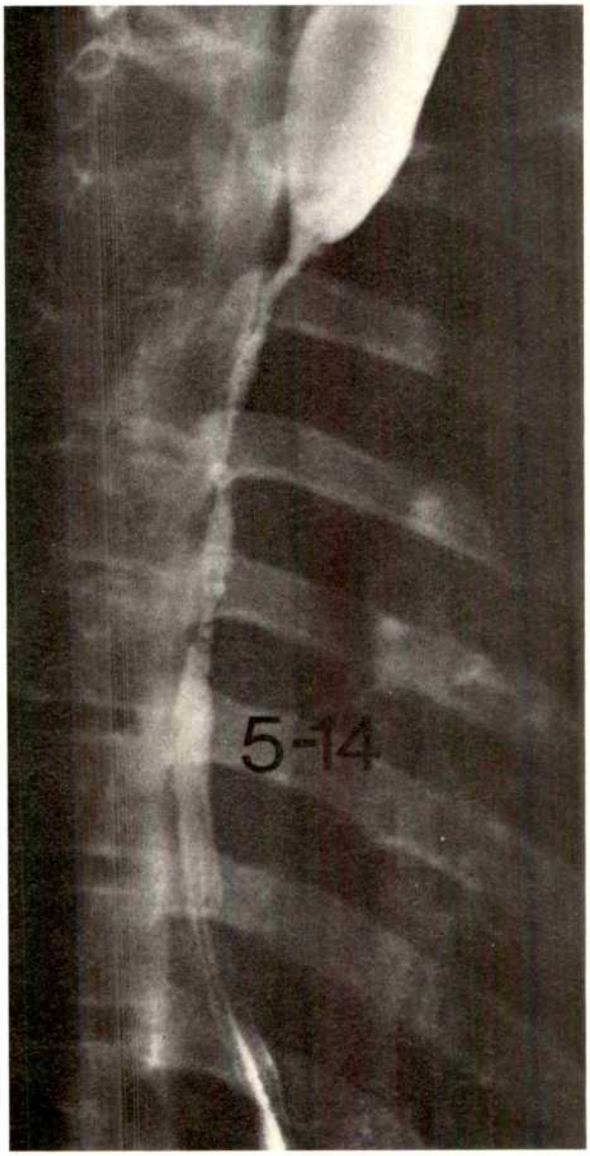


FIG. 2.

Seven weeks later a long, smooth stricture of the middle third of the oesophagus has developed.

firm, culture-proven diagnosis may be difficult to make and therapy may need to be instituted on the basis of the characteristic barium swallow. These features include a shaggy outline, diffuse ulceration, nodular filling defects and diminished peristalsis (Guyer and Brunton, 1971).

Oesophageal narrowing due to mucosal oedema and the presence of a thick pseudomembrane may be an early manifestation of monilial oesophagitis (Kaufman *et al.*, 1960). However, the inflammation may continue and penetrate deeply into the oesophageal wall with subsequent fibrosis and stricture formation. The clinical picture and sequence of events can be very similar to those seen in patients who have ingested lye. Following the onset of acute, painful inflammation there may be a period of several

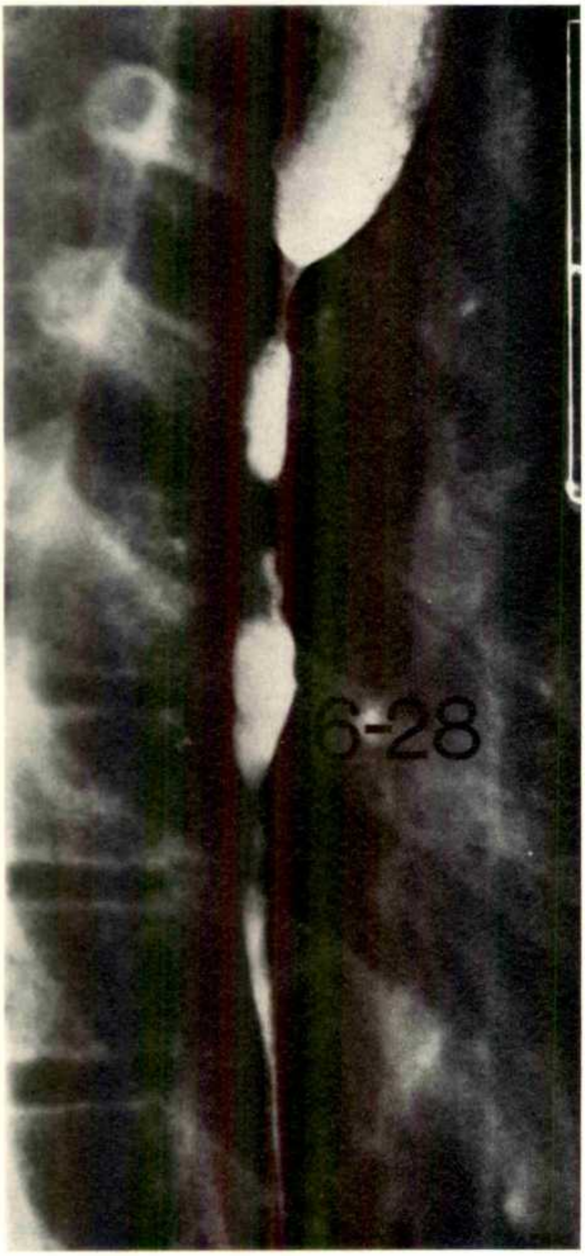


FIG. 3.

Repeat barium swallow six weeks after previous examination demonstrating the stricture to be essentially unchanged.

weeks during which few if any symptoms of oesophageal disease are present. Athey *et al.* (1977) have observed that symptomatic relief may occur before the radiological appearances return to normal. By the time that dysphagia has recurred a permanent and severe oesophageal stricture may already be present, as occurred within seven weeks in our patient. Follow-up barium swallow examinations until the appearances return to normal, even if the patient is asymptomatic, may permit recognition of the insidious development of a stricture. Further therapeutic measures, including a second course of antimonilial therapy or cautious attempts at dilatation, may then be instituted in an effort to prevent this rare but serious complication.

CONCLUSION

A case of persistent oesophageal stricture due to moniliasis, which developed while the patient was symptomatic, is reported. The value and therapeutic implications of performing a repeat barium swallow even if the disease appears to be quiescent are discussed.

REFERENCES

ATHEY, P. A., GOLDSTEIN, H. M., and DODD, G. D., 1977. Radiologic spectrum of opportunistic infections of the upper gastrointestinal tract. *American Journal of Roentgenology*, *129*, 419–425.

GUYER, P. B., and BRUNTON, F. J., 1971. Candidiasis of the oesophagus. *British Journal of Radiology*, *44*, 131–136.

KAUFMAN, S. A., SCHEFF, S., and LEVENE, G., 1960. Esophageal moniliasis. *Radiology*, *75*, 726–731.

ADDENDA

Since this case report was written, two further articles on this subject have been published.

OTT, D. J. and GELFAND, D. W., 1978. Esophageal stricture secondary to candidiasis. *Gastrointestinal Radiology*, *2*, 323–325.

ROHRMANN, C. A. and KIDD, R., 1978. Chronic mucocutaneous candidiasis: radiological abnormalities in the esophagus. *American Journal of Roentgenology*, *130*, 473–476.

1978, *British Journal of Radiology*, *51*, 829–830 OCTOBER 1978

Case reports

Inverted Meckel's diverticulum as a cause of anaemia and continuing blood loss

By J. L. Boldero, B.M., B.Ch., F.R.C.R.

Horton General Hospital, Banbury, Oxon

(*Received March, 1978*)

Inverted or invaginated Meckel's diverticulum is a well recorded cause of intussusception. Ponka (1956) reported two cases and analysed 52 others he found in the literature, and other cases have been reported by Aubrey (1970), Shull and Jones (1975) and Kiprov and Griffel (1975). I have been unable to find a reported case where the inversion of the diverticulum was responsible for blood loss and no acute symptoms were present to suggest that intussusception had occurred.

CASE REPORT

A 26-year-old man was admitted for investigation of anaemia, with a history of possible melaena four to five weeks previously. There had been no dyspepsia, heartburn, or flatulence.

On examination no abnormality was detected. The haemaglobin was 5.3 g/dl, R.B.C. 2.15×10^{12}/l. The blood film showed severe iron deficiency. Occult blood tests were strongly positive. Barium meal, follow-through and enema showed no lesions. Gastroscopy and sigmoidoscopy were also normal. Laparotomy was decided upon, and gastrografin follow-through examination was carried out before operation. This showed a cone shaped filling defect in the distal ileum with serrated edges (Fig. 1); its significance was not certain.

Laparotomy: a small tumour was felt in the terminal ileum two feet from the caecum with a small invagination on the outside of the ileum at the site of the tumour pedicle a quarter of the circumference away from the mesentery. The gut containing the tumour was excised, and an end-to-end anastamosis was performed. Recovery was uneventful. The patient's condition was satisfactory on discharge.

Histology: The tumour was shown to be an inverted Meckel's diverticulum 2 in. (50 mm) in length (Figs. 2 and 3). Microscopy showed that the tip was ulcerated and found to contain a small argentaffinoma.

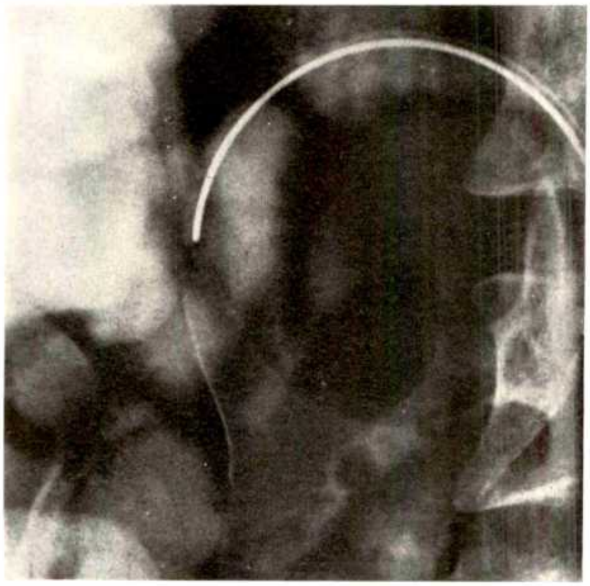


FIG. 1.

Cone-shaped filling defect in distal ileum.

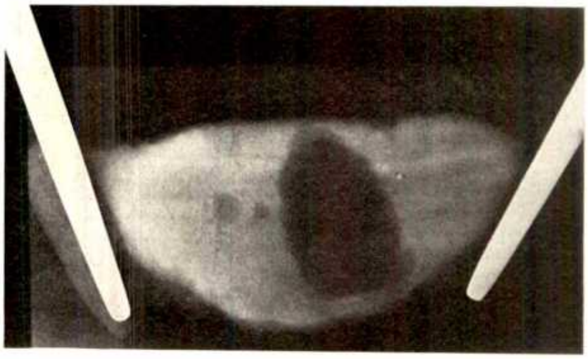


FIG. 2.

Radiograph of injected specimen.

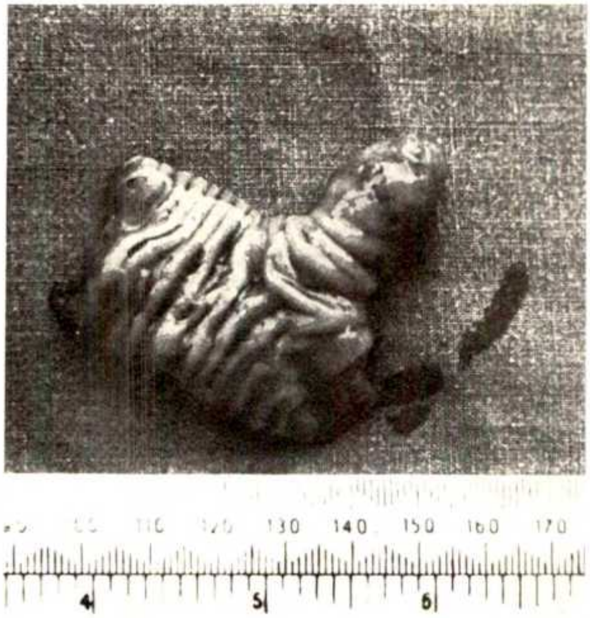


FIG. 3.

Photograph of specimen after inversion of bowel segment.

1978, *British Journal of Radiology*, *51*, 830–831

COMMENT

A Meckel's diverticulum is said to be present in 2% of the population, and various authors have recorded that gastric heterotopia occurs in 10–15% of these diverticula. This is the commonest cause of bleeding, inflammation and perforation in such cases. The present case had no heterotopia, but an argentaffinoma and mucosal ulceration of the inverted tip were present. The inverted diverticulum was demonstrated radiologically although not recognized for what it was.

The patient was under the care of P. W. Fisher, M.R.C.P. and operated on by P. H. Lenton, F.R.C.S.

REFERENCES

AUBREY, D. A., 1970. Meckel's diverticulum. *Archives of Surgery*, *100*, 144–146.

KIPROV, D. D., and GRIFFEL, B., 1975. Inversion of Meckel's diverticulum. *Archives of Surgery*, *110*, 1154.

PONKA, J. L., 1956. Intussusception due to invaginated Meckel's diverticulum. *American Journal of Surgery*, *92*, 545–557.

SHULL, L. N., and JONES, E. E., 1975. Chronic intussusception of Meckel's diverticulum. *Journal of the South Carolina Medical Association*, *71*, 363–365.

A radiographically documented intra-uterine femoral fracture

By E. E. Christensen, M.D., and G. W. Dietz, M.D.

Department of Radiology at Parkland Memorial Hospital and the University of Texas Health Science Center in Dallas, Texas, U.S.A.

(*Received February, 1978*)

Pregnant patients are frequently injured and trauma is now the most common cause of non-obstetrical maternal deaths. In studies done in Minnesota (Barno *et al.*, 1962) and California (Montgomery *et al.*, 1964), approximately 15% of these non-obstetrical deaths were from trauma. Concomitant with the increase in maternal injuries has been a proportionate increase in the incidence of fetal injuries. Crosby (1974) and Buchsbaum (1968) have written review articles on trauma during pregnancy and report fetal fractures of almost every bone in the body. However, we have been unable to find a single report of an intra-uterine fracture through normal bone that was documented radiographically prior to delivery. The following is such a case.

CASE REPORT

This is the story of two patients, a 17-year-old mother and her 37-week-old unborn child. They were in an automobile accident. The mother sustained multiple injuries and she arrived in the emergency room in a deep coma. She had a left closed head injury; the left pupil was dilated and fixed; the right pupil was pinpoint in size; and neither reacted to light. She also had multiple cuts and abrasions with a contusion of the left upper quadrant of her abdomen. The initial impression was a left subdural or epidural haematoma. An immediate craniotomy was indicated. The fetus was not in any acute distress, but a Caesarean section seemed advisable because of the tenuous condition of the mother. Both operations were performed simultaneously.

Several areas were examined radiographically prior to surgery. All of the mother's films, except the abdomen, were normal. The abdominal film (Fig. 1) showed a single intra-uterine pregnancy with cephalic presentation. While examining the distal femoral epiphysis for skeletal maturation, we discovered a femoral fracture (Fig. 2). Survey films following delivery confirmed a fracture of the left femur (Fig. 3). The other fetal bones were normal.

At the time of the Caesarean section, the uterus appeared normal without visible evidence of trauma. The baby, a 3200 g male, did well following delivery except for a brief episode of generalized seizures, thought to be due to cerebral contusion. When last seen, his fracture was healing satisfactorily.

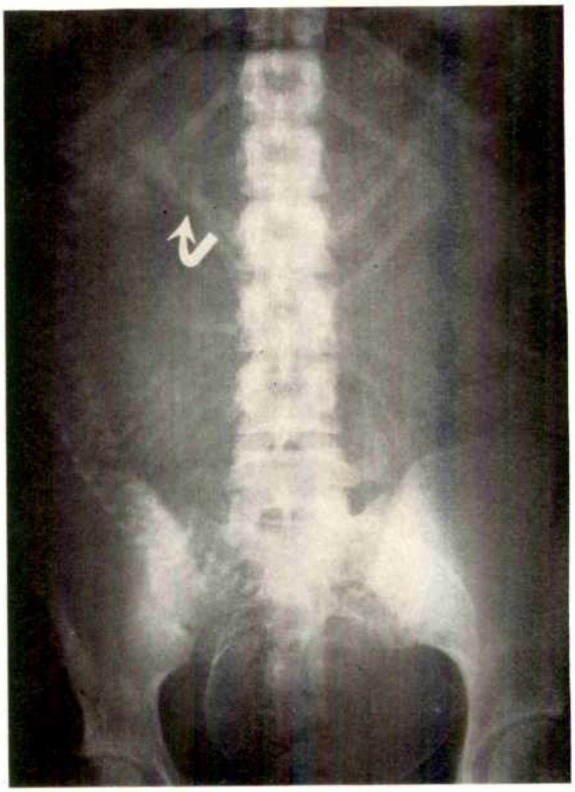


FIG. 1.

Abdominal radiograph showing a near-term pregnancy with a fracture of one of the fetal femora (arrow).

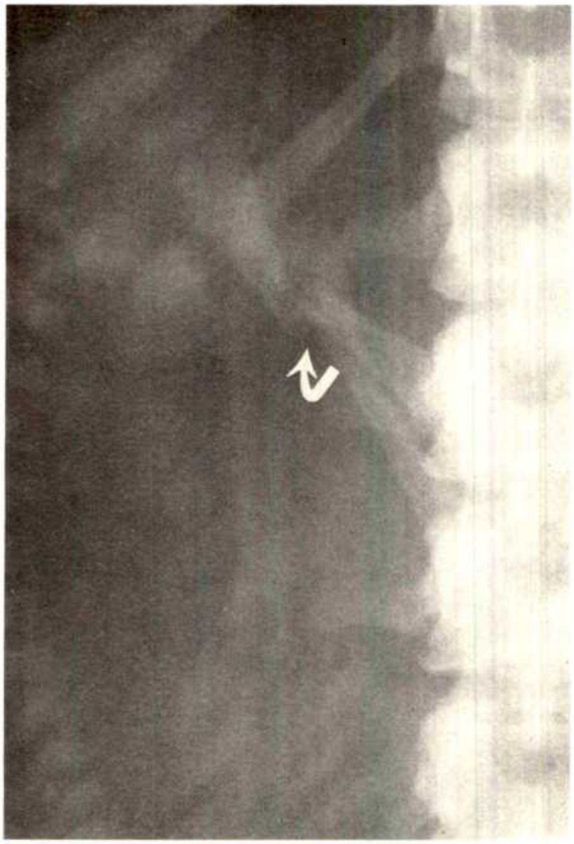


FIG. 2.
Enlargement of the fetus's lower extremities showing the femoral fracture (arrow).

The mother never regained consciousness. At surgery, she was found to have diffuse cerebral oedema. A left decompression craniotomy was performed, but she died on the fifth day following the accident.

DISCUSSION

Early in pregnancy, the fetus is protected by the mother's bony pelvis. Amniotic fluid is proportionately greater in early pregnancy and this fluid buffers the fetus against trauma. Consequently, fetal fractures are most common late in pregnancy when the fetal head is fixed in the pelvis and the buffering effect of the amniotic fluid is diminished. In its fixed position, the head is especially vulnerable to injury, usually from the displaced fragments of a maternal pelvic fracture (Buchsbaum, 1968). The most commonly fractured fetal bones, following the skull, are the clavicles, tibiae and fibulae, humeri and femora. The exact mechanism of injury in our case is unknown, but the fracture is unique in that it was recognized prior to delivery.

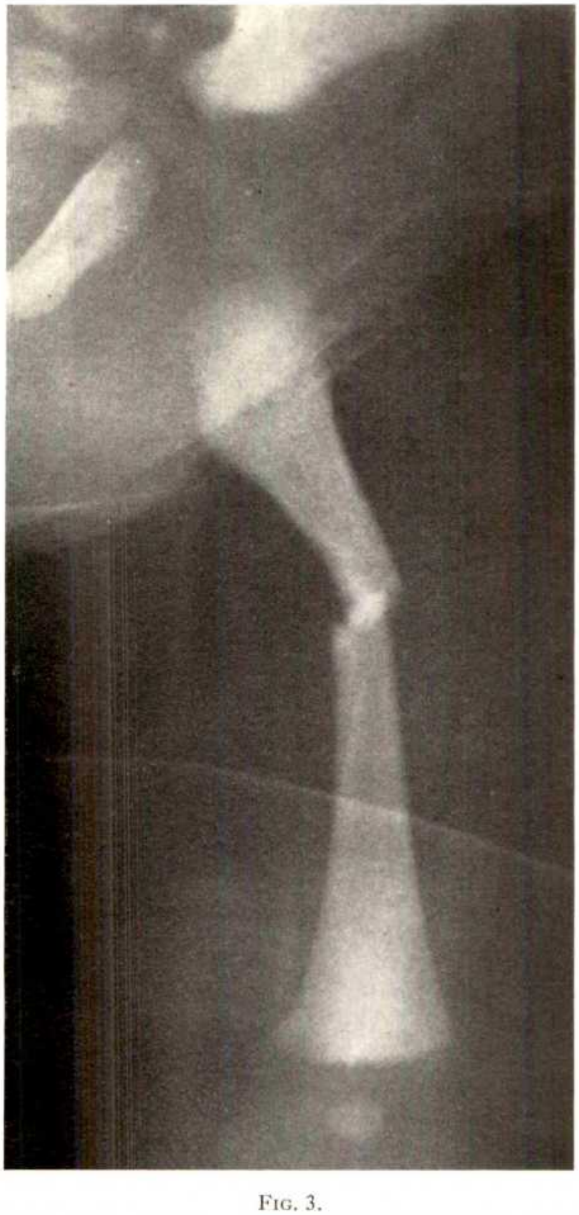


FIG. 3.
Film of the left femur taken after delivery. The bone appears perfectly normal except for the fracture.

REFERENCES

BARNO, A., FREEMAN, D. W., and BAKER, M. P., Jr., 1962. Minnesota mortality study. *Minnesota Medicine*, *45*, 847–853 and 947–955.

BUCHSBAUM, H. J., 1968. Accidental injury complicating pregnancy. *American Journal of Obstetrics and Gynecology*, *102*, 752–769.

CROSBY, W. M., 1974. Trauma during pregnancy: maternal and fetal injury. *Obstetrical and Gynecological Survey*, *29*, 683–699.

MONTGOMERY, T. A., LEWIS, A., and HAMMERSLY, M., 1964. Maternal deaths in California, 1957–1962. *California Medicine*, *100*, 412–421.

1978, *British Journal of Radiology*, *51*, 832–833

Short communication

The effect of vitamin E on cellular survival after X irradiation of lymphoma cells

By K. Fonck, B.Sc. and A. W. T. Konings, Ph,D.

Laboratory of Radiopathology, Bloemsingel 1, University of Groningen, The Netherlands

(*Received April, 1978*)

Little is known about the molecular lesions responsible for cell lethality induced by ionizing radiation in normal and tumour cells. Increased understanding of the mechanisms involved may lead to an enhanced efficacy of radiation therapy. In a recent paper (Konings and Trieling, 1977) we have shown that lymphosarcoma cells grown in vitamin E deficient mice are more radiosensitive than tumour cells grown in normal mice. It appeared from these experiments that the membranes of the vitamin E depleted tumour cells were more vulnerable to lipid peroxidation. These experiments were suggestive of membrane involvement in radiation-induced cell death. In the present report we provide further evidence on the protective ability of vitamin E against radiation damage.

TECHNIQUES

A lymphocytic mouse leukaemic cell line L5178Y was routinely grown in suspension cultures. The medium consisted of RPMI 1640 (Flow, Irvine, Scotland), 10% fetal calf serum (Gibco, Glasgow, Scotland), 2 μg/ml streptomycin, 500 IU/ml penicillin G. If added, vitamin E was at a concentration of 100 μg/ml. At 37°C the population doubling time was about 12 hours in both culture conditions. Asynchronous cultures were irradiated at a cell density of 2×10^6–4×10^6 cells/ml while air (+5%CO_2) or nitrogen (+5%CO_2) was bubbled through the suspensions. The irradiation was performed with a Philips-Müller MG 300 X-ray machine operated at 200 kV and 15 mA at a dose-rate of about 6.75 Gy/min at 20 cm FSD. The beam was filtered by 0.2 mm Cu. The cells were plated out directly after irradiation on 0.3–0.5% soft agar in RPMI medium plus 20% fetal calf serum. Cell survival was determined 7 to 10 days later by counting colonies.

RESULTS AND DISCUSSION

It can be seen in Table I that the survival characteristics did not change when vitamin E was present during the irradiation of normally grown cells. However, cells grown for several weeks in a vitamin E enriched medium appeared to be less radiosensitive as a quasi-threshold dose *Dq* was observed in these cell lines. The exponential slope as described by the parameter *Do* had not changed however. A typical experiment is shown in Fig. 1. Almost no shoulder in the survival curve was present when the cells were grown under normal conditions (Fig. 1A). A clear shoulder appeared in the vitamin E line (Fig. 1B).

The cells irradiated under oxic and hypoxic conditions have the same extrapolation number of about two; so oxygen is strictly "dose-multiplying" in the vitamin E enriched cells. The fact that the presence of vitamin E only during irradiation does not protect the cell suggests that the compound has to be incorporated into the membranes of the cell. From experiments with model systems of liposomes, we learned that vitamin E can very effectively protect polyunsaturated fatty acids against radiation damage when incorporated into the membrane (Konings *et al.*, 1978). Since the work of Elkind and Sutton (1960), the presence of a shoulder on a survival curve has been interpreted as an accumulation of sub-lethal damage. No change in final sensitivity to lethal events is observed in our vitamin E enriched cells; the curves had approximately similar slopes. This would mean that the cells had changed with respect to their ability to determine whether a damaging event shall be "lethal" or "sublethal".

Although no fractionation experiments have been performed as yet, these results are very suggestive of an increased ability to repair radiation damage. Stabilization of the cellular membranes by vitamin E may play a role in this mechanism. The possibility of biological membranes being critical targets in irradiated cells has been mentioned before by Alper (1963; 1971; 1974). There is some experimental evidence that the peripheral region of the cell nucleus is the most sensitive part of the cell (Zermeno and Cole, 1969; Datta *et al.*, 1976). Some new evidence has been reported on the role of the nuclear membrane in DNA replication (Hobart *et al.*, 1977). It was proposed by Alper (1963; 1971; 1974) that cell killing by ionizing radiation is due to N type (DNA) and O type (membrane) damage. If vitamin E especially protects the membranes against radiation damage, then the constancy of the oxygen enhancement ratio (OER) in both systems (Table I), might mean a fixed balance between the targets proposed. Studies are in progress to verify the suggested involvement of the nuclear membrane in the phenomenon of vitamin E-induced repair of sublethal damage.

ACKNOWLEDGMENTS

We thank Mr. Coultas, MRC, Hammersmith Hospital, London, for providing the L5178Y cells and making us

TABLE I

THE EFFECT OF VITAMIN E ON SURVIVAL CHARACTERISTICS OF L5178Y

Vitamin E present during: Growth	Irrad.	Post-irrad.	*Do* n	*Do* Air	*Do* N_2	OER	*Dq* Air	*Dq* N_2
—	—	—	(6)	0.97±0.10	2.18±0.25	2.3±0.3	0	0
—	+	—	(2)	1.04	1.99	1.9	0	0
+	+	—	(2)	1.01	2.22	2.2	0.70	1.60
+	+	+	(4)	0.88±0.05	1.73±0.19	2.0±0.2	0.76±0.29	1.08±0.32

n: number of experiments; the error shown is the standard deviation. Dose in Gy.

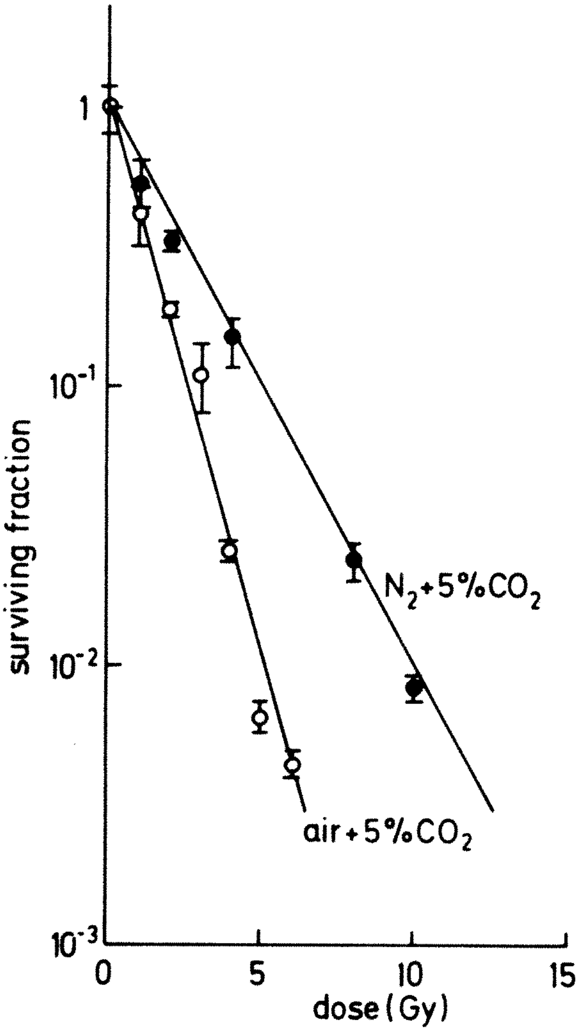


FIG. 1A.

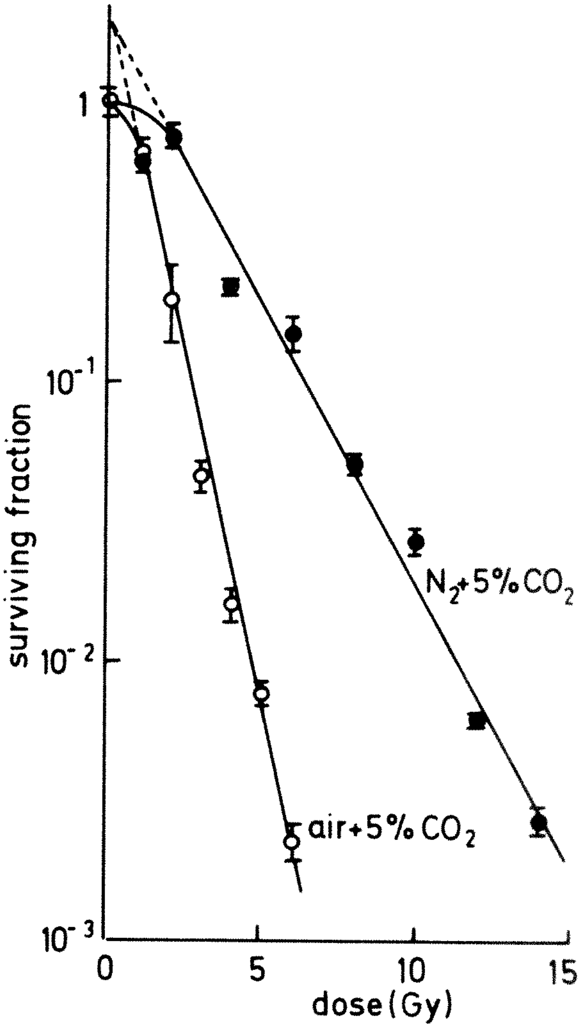


FIG. 1B.

FIG. 1A. Survival curves of L5178Y cells grown in a normal culture medium: ○, oxic conditions; ●, hypoxic conditions. Each point represents the mean ± standard deviation.

FIG. 1B. Survival curves of L5178Y cells grown and irradiated in a medium supplemented with vitamin E (100 μg/ml).

familiar with the irradiation set up. Miss Els Drijver is gratefully acknowledged for technical assistance. Financial support for these studies was obtained from the IRS, Interuniversity Institute for Radiopathology and Radiation Protection in the Netherlands.

REFERENCES

ALPER, T., 1963. Lethal mutations and cell death. *Physics in Medicine and Biology*, *8*, 365–385.

1971. Cell death and its modification: the role of primary lesions in membranes and DNA. In *Biophysical aspects of radiation quality*, IAEA, Vienna, p.171.

1974. The role of membrane damage to irradiated cells. *British Journal of Radiology*, *47*, 240.

DATTA, R., COLE, A., and ROBINSON, S., 1976. Use of track-end alpha particles from ^{241}Am to study radiosensitive sites in CHO cells. *Radiation Research*, *65*, 139–151.

ELKIND, M. N., and SUTTON, H., 1960. Radiation response of mammalian cells grown in culture. I. Repair of X-ray damage in surviving Chinese hamster cells. *Radiation Research*, *13*, 556–593.

HOBART, P., DUNCAN, R., and INFANTE, A. A., 1977. Association of DNA synthesis with the nuclear membrane in sea urchin embryos. *Nature*, *267*, 542–544.

KONINGS, A. W. T., and TRIELING, W. B., 1977. The inhibition of DNA synthesis in vitamin E depleted lymphosarcoma cells by X rays and cytostatics. *International Journal of Radiation Biology*, *31*, 397–400.

KONINGS, A. W. T., DAMEN, J., and TRIELING, W. B., 1978. Protection of liposomal lipids against radiation induced oxidative damage. *International Journal of Radiation Biology* (in press).

ZERMENO, A., and COLE, A., 1969. Radiosensitive structure of metaphase and interphase hamster cells as studied by low-voltage electron beam irradiation. *Radiation Research*, *39*, 669–684.

1978, *British Journal of Radiology*, *51*, 834–835

Education in, and status of, radiology in Europe

The European Association of Radiology has been anxious to help to establish the status of radiology throughout European countries. The standing of radiologists in many European countries is not the same as in Britain where consultants in one recognized specialty are the equal of consultants in other specialties.

In Britain, nowadays, a candidate for a consultant post should ideally possess the Fellowship of the Royal College of Radiologists, and will probably have five or six years of experience of radiology behind him.

In other European countries an examination system has not been developed, and training in most branches of medicine has been by apprenticeship. France and Eire have well established examination systems in radiology and more recently Italy and Switzerland have introduced them.

Because of this, countries in the European Association have been anxious to emulate the British system. Discussions started three years ago in Bordeaux, continued in Bristol and Brussels, later in Athens and London, leading to a detailed logistical analysis in Bath, in August, 1977; these were followed by a plenary session consisting of representatives from all the countries in the European Association in Hamburg in December, 1977. At this latter meeting, apart from minor modifications, full agreement on European Diplomas in Radiology, one in Radiodiagnosis and one in Radiotherapy and Oncology, on the syllabus for each, on the need for basic requirements in training departments and on the method of examining, were all agreed by representatives from the member countries. Those countries were: Austria, Belgium, Britain, Denmark, East Germany, Eire, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden and Switzerland. Czechoslovakia, Poland and Yugoslavia have also expressed interest.

The syllabus and the examination structure, in so far as it is possible to establish patterns in a multinational system, have been based on the British Fellowship of the Royal College of Radiologists. Inevitably, in preparing a multilingual approach to education based on the pattern of one country, difficulties arise. And inevitably in putting this bold project into practice more difficulties will be encountered. One of the greatest difficulties to overcome will be the sad recent death of Professor van der Schueren of Louvain University, who had the unique privilege of being both Professor of Radiotherapy and Professor of Anatomy at the University of Louvain, and who was the driving force in the creation of this educational advance.

Quite what the significance of the European diploma is going to be in Britain with its tradition of extremely highly trained radiologists and its tradition of steep academic hurdles to be overcome on the way, is unclear at present. Certainly in the European Community or anywhere else in the world, Fellowship of the Royal College of Radiologists is a passport to any radiological appointment. Whether the reverse will be true, *i.e.* whether possession of the European diploma will enable the individual to to be a serious candidate for a consultancy in the N.H.S., must await the assessment of time. Standards must be judged. It took 15 years from 1939 for the F.F.R. (later F.R.C.R.) to establish itself. However, there was no doubt whatsoever at the Hamburg meeting in December, 1977, that all the other European countries were determined to introduce this system and also keenly wished to be guided by persons from this country in the conduct of educational programmes and assessment along these lines. Undoubtedly our European colleagues believe that this will both improve their educational methods and improve the status of Radiology in the respective countries. At the Hamburg meeting the following prepared statement was agreed:

> The European Association of Radiology, representing the national societies of the member countries, has planned to establish a Diploma in Radiology which can be taken in either Radiodiagnosis or in Radiotherapy and Oncology. The intention is that the Diploma should represent a guarantee of a high level of training and qualification. The Diploma will be obtainable by examination. The Commission on Education of the European Association has drawn up a syllabus, consisting of a tronc commun and separate branches of knowledge in the two fields. Radiologists who have completed four years of training in one of the two specialties and who have been recognized as specialists by their own national society are eligible.

The E.A.R. has set up a Board of Examiners and the examination will consist of a written and an oral part. Applications for the first examination, which will take place in March, 1979, simultaneously in all the countries concerned, must be received by the National Society before 30th September, 1978. Full details of the syllabus requirements and examinations can be obtained from the National Society.

In Britain, so far as European and International Radiology is concerned, the "National Society" is the Royal College of Radiologists and the British Institute of Radiology jointly.

The proposed Diploma, its syllabus and examination, have been considered by the Royal College of Radiologists and it has been decided that, in view of the fact that the College is already heavily committed in running its own Fellowship examinations in both radiodiagnosis and radiotherapy, examinations held twice a year, both for the first examination and the final examination in each discipline, involving an immense amount of work on the part of the College secretariat, the College will support in principle the commencement of examinations for the European Diploma in Radiology, but could not yet participate in running these examinations in the United Kingdom.

European Association of Radiology.

Book reviews

Introduction to Nuclear Radiation Detectors. By P. J. Ouseph, pp. xii+194, 1975 (Plenum Press: New York and London), $24.20.

The dust cover of this book claims it to be "a complete guide to the operation of radiation counters". Based on a lecture course for science, engineering, medical and dental students it is clearly written at the right level. It opens with a brief survey of nuclear radiations (including neutrons) and their interactions with matter. Three main types of detector are then described: gas, scintillation and semiconductor, the treatment of γ-spectrometry being particularly lucid. The book closes with a chapter on corrections in radiation counting. The emphasis is on the principles of the subject and few mistakes or typographical errors were found. However, a book of this nature should use SI units, particularly in the definition of the roentgen.

It is easy to criticize a book for its omissions, especially when brevity has understandably been in the author's mind. Nevertheless many biomedical readers will be disappointed that little guidance is given as to the choice and use of the detectors. It would have been improved with more practical examples. The final chapter on "corrections" is particularly disappointing. Dead time and lost counts corrections are hidden in another chapter under the name "coincidence losses", and there is no mention anywhere of problems of sample preparation and the necessity for quench corrections in liquid scintillation counting.

Overall a clear and well presented exposition of the subject, but its limitations will restrict its usefulness for readers of this journal.

B. P. Parker.

Traite de Radiodiagnostic. Tome XIX, Radiopediatrie. Thorax—appareil respiratoire et appareil cardio-vasculaire. By J. Lefebvre, pp. xviii+801, 1978 (Masson Editions, Paris), F.890.

This is one of a series of 20 volumes (3 in 2 parts) dealing with the whole of radiology. This volume deals with the thorax, the thoracic wall, the lungs, mediastinum and heart. The first 36 pages which deal with methods of examination, plain film, tomography, bronchography, isotopes and angiography are too sketchy to be of value. The next 47 pages describe the embryology and anatomy of the heart and lungs. The section of the heart is excellent. It was disappointing in a book of this size, however, not to see a description of bronchial anatomy or of the lobes of the lungs. The book excels in the next two sections, which in effect are the equivalents of a book on the lungs (407 pages) and on the heart (297 pages). The illustrations are small but clear and well annotated. Congenital and acquired lesions are extensively discussed, the only strange omission being rheumatic heart disease. The book is beautifully produced on glossy paper. There is a good list of references at the end of each chapter mainly from the American and French literature. An English translation is promised soon.

The authors have succeeded in producing a very good reference book on the paediatric thorax. It is very expensive at over £100: but the wealthy purchaser may console himself with the fact that he has virtually bought two books for the price of one.

G. M. Steiner.

1978, *British Journal of Radiology*, *51*, 836–837

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Absorbed radiation dose in radiation synovectomy

THE EDITOR—SIR,

The intra-articular injection of colloids containing β-particle emitting radionuclides has been shown to help in controlling synovial inflammation in a range of joints (Ansell *et al.*, 1963; Grahame *et al.*, 1970; Gumpel, 1973; Menkes *et al.*, 1977), and in the knee Gumpel and Coles (1975) have shown the technique to be the treatment of choice for the older patient.

TABLE I

PHYSICAL PROPERTIES AFFECTING THE DOSIMETRY

Radionuclide	Half-life (days)	β Radiation	
		Maximum energy (MeV)	Average number per disintegration
^{90}Y	2.67	2.27	1.00
^{186}Re	3.70	1.07 0.934	0.74 0.21
^{169}Er	9.6	0.340 0.332	0.58 0.42

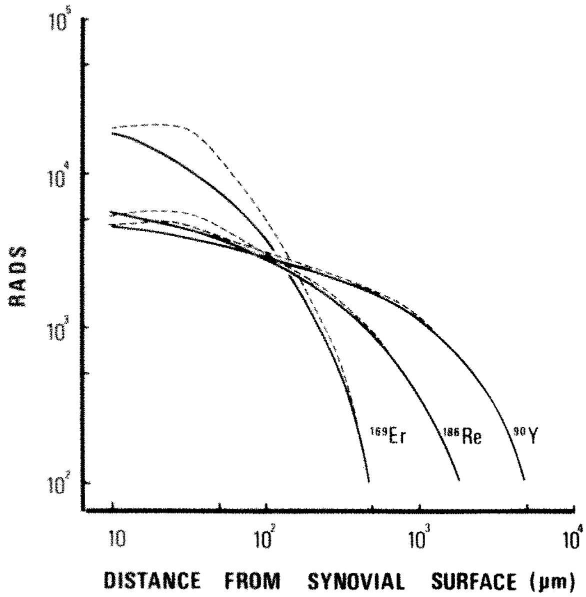


FIG. 1.

The radiation dose from a plane source of infinite extent as a function of distance from the source. The solid lines show the dose for an infinitely thin surface layer of the radionuclides and the dotted lines show the dose when the nuclide is distributed uniformly through a surface layer 40 μm thick. The concentration of the radionuclides is 1 mCi/250 cm^2.

Originally the only suitable radionuclides available in colloid form were ^{198}Au and ^{90}Y but colloids of ^{186}Re and ^{169}Er are now also readily obtainable and have largely replaced the use of ^{198}Au. At present ^{90}Y is used primarily for the knee and ^{169}Er primarily for the finger joints, while ^{186}Re is used for the joints of intermediate size (Menkes *et al.*, 1977). The amount of radioactivity that is required in order to achieve a specific radiation dose to the synovium of a given joint cannot however be accurately determined for several reasons. The surface area and thickness of the synovium are not accurately known, it is not known how much of the injected dose will be taken up by fibrin deposits in the synovial fluid instead of by the membrane, and it is not known how much of the administered radioactivity will leak out from the joint cavity (Prichard *et al.*, 1970). Because of these difficulties standard doses of the radionuclides have been used for the treatment. The purpose of this letter is to show the relative radiation dose produced by the β-particles from the radioactive decay of ^{90}Y, ^{169}Er and ^{186}Re, the three colloids currently in most general use.

Following intra-articular injection the colloid has been shown to be taken up by phagocytosis into cells on the surface of the synovial membrane and not to reach the deeper supporting parts (Webb *et al.*, 1969). In order to model this situation the radiation dose has been calculated at different distances from a thin plane source of infinite extent (the surface of the synovium) for each radionuclide and the effect of varying the thickness of the source has also been investigated. The method used for the calculation was that of Leovinger *et al.*, (1956). The results obtained for ^{90}Y agree with those already published for this radionuclide by Husak *et al.*, (1973) and are included for comparison with the results on the other two radionuclides.

The physical properties of the radionuclides which affect the radiation dose are shown in Table I; the γ rays emitted in the decay of ^{186}Re and ^{169}Er have been omitted because their contribution to the radiation dose is negligible (less than 1% of the β dose at 1000 μm). The calculated fall off in the absorbed dose with distance from the plane source for each radionuclide is shown in Fig. 1. As is anticipated from the energy of the β particles emitted, the radiation from ^{169}Er has the fastest fall off with distance while that from ^{90}Y has the largest long range effect. The increase in dose occurring when the colloid is uniformly distributed through a thickness of 40 μm (corresponding approximately to the thickness of one or two layers of cells) is also greatest for ^{169}Er. More surprisingly, perhaps, the radiation dose per mCi at small distances is approximately a factor of four higher for ^{169}Er than it is for the other radionuclides and this is due both to its lower β particle energy and its longer radioactive half-life.

Although this information is not of direct help in the problem of determining the radiation dose in any one joint it does enable the effect of the use of the different colloids to be compared. We have found it to be of assistance in the decision as to which colloid to use in any particular joint and in determining the amount of radioactivity to administer.

Yours, etc.

C. S. BOWRING,
D. H. KEELING.

Departments of Medical Physics and Nuclear Medicine,
Plymouth General Hospital,
Freedom Fields, Plymouth.

REFERENCES

ANSELL, B. M., CROOK, A., MALLARD, J. R., and BYWATERS, E. G. L., 1963. Evaluation of intra-articular colloidal gold

^{198}Au in the treatment of persistent knee effusions. *Annals of the Rheumatic Diseases*, *22*, 435–439.

GRAHAME, R., RAMSEY, N. W., and SCOTT, J. T., 1970. Radioactive colloidal gold in chronic knee effusions with Baker's cyst formation. *Annals of the Rheumatic Diseases*, *29*, 159–163.

GUMPEL, J. M., 1973. Symposium on radioactive colloids in the treatment of arthritis. *Annals of the Rheumatic Diseases*, *32*, Supplement to No. 6.

GUMPEL, J. M., and COLES, N. C., 1975. A controlled trial of intra-articular radiocolloids versus surgical synovectomy in persistent synovitis. *Lancet*, *1*, 488–489.

HUSAK, V., WIEDERMANN, M., and KRAL, M., 1973. Absorbed dose due to beta rays from radioactive colloids in radiation synovectomy. *Physics in Medicine and Biology*, *18*, 848–854.

LOEVINGER, R., JAPHA, E. M., and BROWNELL, G. L., 1956. Discrete radiosiotope sources. *Radiation Dosimetry* p. 719–730. Ed. by G. J. Hine and G. L. Brownell. (Academic Press, New York.)

MENKES, C. J., LE GO, A., VERRIER, P., AIGNAN, M., and DELBARRE, F., 1977. Double blind study of erbium 169 injection (synoviorthesis) in rheumatoid digital joints. *Annals of the Rheumatic Diseases*, *36*, 254–256.

PRICHARD, H. L., BRIDGMAN, J. F., and BLEEHEN, N. M., (1970). An investigation of radioactive yttrium (^{90}Y) for the treatment of chronic knee effusions. *British Journal of Radiology*, *43*, 466–470.

WEBB, F. W. S., LOWE, J., and BLUESTONE, R., (1969). Uptake of colloidal radioactive yttrium by synovial membrane. *Annals of the Rheumatic Diseases*, *28*, 300–302.

Radiation protection in dentistry

THE EDITOR—SIR,

Any discussion of possible changes in radiation protection in the dentist's surgery must of necessity be tentative until the NRPB reports to the Health and Safety Executive the results of its present survey into current practice. Nonetheless, there are a number of points in Mr. Gifford's review of the WHO Manual on Radiation Protection in Dentistry (January, 1978, p. 57) that deserve further comment.

Mr. Gifford distinguishes three situations in dental radiography which he regards as the most hazardous. The first relates to the risk to those members of the dentist's staff, other than those directly involved in radiography (that is the dentist himself and his surgery assistant), from scattered radiation. It is difficult to visualize a situation in which the layout of the surgery puts those outside at greater risk than those within when a standard dental X-ray set is used. On the other hand the introduction of panoramic radiography into general dental practice may have so markedly increased workloads that more attention will have to be paid to structural shielding. The Dental Estimates Board are also concerned at the way in which the widespread application of this technique has generated a massive increase in payments to practitioners. In an effort to reduce this expenditure the Board have substantially curtailed the permitted indications for panoramic radiographs. Under these circumstances there may be a marked fall in the number of these radiographs taken in general dental practice.

Second, Mr. Gifford would have us abandon mechanical timers. The three essential requirements for timers are defined in para. 4.2.6 of Radiological Protection in Dental Practice (1975), the general dental practitioners' vademecum in these matters. There is no advice specifically that electronic timers are to be preferred.

Third, Mr. Gifford deprecates the practice of holding the film in the patient's mouth. Since he qualifies this practice as "now unusual" he must imply the dentist as the holder. If, as Mr. Gifford agrees, this practice is now unusual, then perhaps this particular sentiment should be peacefully buried: instead, it might be more salutary to consider the current situation in periapical radiography where the patient retains the film packet in position with a finger. Radiological Protection in Dental Practice (para. 3.2.2(f)) advises against this.

This technique is possible under certain circumstances: the long-cone paralleling procedure requires an excitation potential of 75 kV (contrary to Mr. Gifford's estimate of its rarity, this technique is taught at the Glasgow Dental School); alternatively the Rinn XCP device can be attached, for example, to the Philips Oralix. However, the majority of dentists in this country use the bisecting angle technique. Image quality with this technique depends in part, as a consequence of the short FFD, on the smallest possible object–film distance. A film holder negates this basic principle (with the one exception of the mandibular molar region).

Mr. Gifford points out the risk, in any discussion of radiation hazards in dentistry, of creating needless alarm for the patient. He also alludes to the difficulty of supervising standards in general dental practice. Smith (1978) has noted the high level of voluntary co-operation provided by dentists in the NRPB's current postal pack survey. He has also drawn attention to the possible discrepancy between the extent of this radiation hazard and of non-industrial accidents in the home and on the roads. Dentists in this country tend to use radiography less than they might; it would be unfortunate if the pursuit of radiation safety inhibited them further and resulted instead in the referral of their patients to their local hospital department of radiodiagnosis.

Yours, etc.,
P. N. HIRSCHMANN.

University Dental Hospital of Manchester,
Bridgeford Street,
Manchester M15 6FH.

REFERENCES

Department of Health and Social Security (1975) Radiological Protection in Dental Practice.

SMITH, N. J. D., 1978. Radiation protection. The administrative and legal framework in the United Kingdom. *British Dental Journal*, *144*, 47–45.

W.H.O., 1978. Manual on radiation protection in dentistry, p.57.

CAT stimulation of retina

THE EDITOR—SIR,

I recently underwent an Emiscan (fortunately negative) at the skilled hands of Professor George du Boulay, and it confirmed an observation that I made in 1922, that the retina can be stimulated by X rays.

In 1922 I removed a screen from a couch and in the dark made a brief exposure (a practice I do not recommend!). While I overlooked the screen carriage I observed a bright flash.

Last week, when in the Emiscan machine, my eyes were tightly bandaged and completely blacked-out. However, each time the Emiscan traversed my eyes I saw a glow of light. Scanning above and below the level of the eyes produced no sensation of vision.

Yours, etc.,
S. COCHRANE SHANKS.

11 Wimpole Street,
London W1M 7AB.

1978, *British Journal of Radiology*, *51*, 838–840

Proceedings of The British Institute of Radiology

The theory and practice of data display

Abstracts of papers presented at the joint meeting of the Institution of Electronic and Radio Engineers, the Institute of Electrical Engineers, the Hospital Physicists' Association, British Pattern Recognition Association, The British Institute of Radiology and the Electrical Trades Association on February 13, 1978 at the Royal Institution, Albemarle Street, London W.1.

Seeing objects under difficult condition, by F. W. Campbell.
Colour in data display, by D. Pavey.
Physical parameters used to assess image quality, by P. F. Sharp.
The quality of a good diagnostic clinical image, by T. Healey.
Multichannel displays for physiological data, by G. H. Dyford.
Clinical quality in nuclear medicine: ROC analysis and its role, by P. Vernon.
Dynamic displays in nuclear medicine, by B. A. Goddard.
Computerized tomography: photon quantum limits in image quality, by J. N. A. Ridyard.
Diagnostic optimization, by K. E. Britton.
The thermographic image, by E. F. J. Ring.

Reprints of these abstracts may be obtained free on application to the Managing Editor, The British Journal of Radiology 32 Welbeck Street, London W1M 7PG, tel. 01–935 6867.

SEEING OBJECTS UNDER DIFFICULT CONDITIONS

By F. W. Campbell

The Physiological Laboratory, Cambridge

Recently there has been a much better understanding of how the human visual system perceives objects of different sizes and shapes under conditions of low contrast and/or camouflage. A number of demonstrations were given to illustrate the main factors involved.

COLOUR IN DATA DISPLAY

By D. Pavey

Kingston Polytechnic

Some of the colour conventions and usages of the designer do appear to be related to physiological optics, but a designer will only be able to realize the full information-potential of colour if he understands its parameters (hue, luminance and intensity), their relation to field contrast and the comparative strength and surface quality of the colour signal. As an aspect of what a designer calls "impact", signal strength is not just another parameter of colour but a function of all three. Levels of impact can be arrayed on a stimulus/arousal gradient, giving the designer a whole range of possible information quanta, capable of conveying quite complex model data appropriate to various hierarchies of effect and to specific categories of information.

PHYSICAL PARAMETERS USED TO ASSESS IMAGE QUALITY

By P. F. Sharp

University of Aberdeen

The problems of assessing image quality are outlined by reference to display systems used in clinical radionuclide imaging. Here the observer is not only faced with the usual problem of deciding what are the normal features of the image and what are abnormal, but he must also deal with images having a relatively low photon density, usually only a few hundred photons per sq. cm.

In this field of imaging two psychophysical methods have mainly been used to measure image quality, namely the method of constant stimulus and signal detection theory. The way in which each method seeks to produce parameters to measure the possibility of discriminating between signal and noise was outlined and the advantages and disadvantages of each approach were described.

The practical application of these methods to the problems of assessing display performance and the effect of image processing was demonstrated.

THE QUALITY OF A GOOD DIAGNOSTIC CLINICAL IMAGE

By T. Healey

Barnsley District General Hospital

Quality in a medical diagnostic image is not an absolute attribute that can be created in a laboratory or can even be monitored there, because quality control in medical work must be individual with 100% sampling. Sometimes, when the patient is desperately ill, we must be satisfied with less full information, but under all circumstances we should maximize our chances of making an accurate diagnosis, which usually means that we should standardize our image-forming exposure factors and our processing cycle. This necessitates that the equipment really does give the performance suggested by its design specifications. An apparatus to check this performance was described.

Processing remains important in diagnostic radiology, though less so in ultrasonic and isotope imaging and with CAT scanning. Some defects of placing undue emphasis on rapidity of processing rather than on the quality of the diagnostic image were discussed. Finally, advice was given on the selection of viewing conditions to make the best use of the diagnostic information in the image.

MULTICHANNEL DISPLAYS FOR PHYSIOLOGICAL DATA

By G. H. Dyford

RAF Institute of Aviation Medicine

There is perhaps no single signal source which requires more different kinds of measurement than a biological preparation, and almost invariably there is the need to correlate physiological observations either with other biological variables or with a physical stimulus responsible for changes in physiological state. Hitherto the most popular multichannel display has been the pen recorder, having from two to thirty or more simultaneous writing channels; the information in such recordings is undeniably greater than that which is actually extracted from them. The most pressing biological display problem resolves itself into two clear divisions;

1. Methods of display which are able to show both the individual channels and relationships between them, and
2. The development of mathematical or empirical processes which reduce the data to manageable proportions.

It is rarely the case that a pictorial display is neither essential nor desirable. The value of statistical methods is indisputable and there is much new work both in stationary and non-stationary time series; but how can we display statistical results when they may be a dynamic function of more than one variable. Three-dimensional displays of varying degrees of complexity are available but expensive of computer time. Colour has been employed and is superficially attractive, but there are considerable dangers; colour has a powerful separating influence, and it may be that such separation does more harm than good; we have yet to learn how to interpret changes of shade, and dynamic colour mixtures.

CLINICAL QUALITY IN NUCLEAR MEDICINE: ROC ANALYSIS AND ITS ROLE

By P. Vernon

Charing Cross Hospital

Nuclear medicine images suffer from several forms of degradation, the most significant being statistical noise due to the small number of photons forming each image. Poor focus of the X rays and distortion are also present. A wide range of analogue and digital processing techniques are used to enhance the images so as to direct the attention of the observer to information which is of clinical interest. The type of image presentation chosen will depend on the clinical situation. The most frequently employed operations are (1) smoothing or blurring to reduce statistical noise, (2) corrections for known distortions, and (3) filtering or refocusing to enhance resolution or contrast. A great number of filters have been tested in the nuclear medicine field, principally of the Wiener type, and some very simple but highly effective filters have found wide usage, most notably the Canterbury filter. Pattern recognition techniques have not been very successful when applied to nuclear medicine, although recent work using principal component analysis is very encouraging.

Assessing the usefulness of any image processing is often difficult because of the wide range of information which may be wanted from an image, and the range of experience and sensitivity of the observers. ROC analysis is a powerful technique for obtaining an objective measure of the value of image enhancement, eliminating the variations in observers. Unfortunately it cannot be applied to all the problems of image display found in nuclear medicine.

DYNAMIC DISPLAYS IN NUCLEAR MEDICINE

By B. A. Goddard

Southampton General Hospital

Cardiac studies in nuclear medicine have brought increased complexity to the subject, both in the acquisition of data and its analysis. The use of an on-line computer with the scintillation camera is mandatory in the technique and rapid developments are taking place.

Acquisition and display methods were described, and some of the problems presented by the requirements of this fast dynamic study were discussed.

COMPUTERIZED TOMOGRAPHY: PHOTON QUANTUM LIMITS IN IMAGE QUALITY

By J. N. A. Ridyard

EMI Medical Ltd

The information contained in a computerized tomography image is fundamentally constrained by the number of X-ray photons in a clinically acceptable radiation dose. The present performance of CT instrumentation is remarkably close to that projected by theory. It is important, however, to pay attention to the spatial coding and decoding methods as well as various design refinements if the information transfer is to be as complete as possible. The relations between dose and the image quality were described, and the trading rules illustrated. Comparison was also made with the alternative coding and decoding technologies. The clinical benefits, both as regards diagnostic ability and through-put of patients, were also be related to the type of technology.

DIAGNOSTIC OPTIMIZATION

By K. E. Britton

St. Bartholomew's Hospital

If the "nul hypothesis" of clinical management is to watch and wait, then any benefit from the result of a test could and probably should be judged in terms of its influence on clinical action on the patient's behalf, as an alternative to a watch-and-wait policy. In these terms, a test result which helps to make a diagnosis but which does not alter clinical management has a lower order of importance than one that causes or changes clinical action. This leads to the view that differential management should be our aim and not differential diagnosis. The ordering of all investigations possible in a clinical speciality (for example all *in vivo* investigations applicable to the liver) on all patients attending the specialist, might also be construed as the "nul hypothesis" of diagnosis. Against this hypothesis, various strategies and tactics may be evaluated which align tests in some order of flow, so that the results of one test lead logically to action or a request for the next. Criteria for such strategies include: the use of a non-invasive and/or less expensive test before an invasive and/or more expensive test; the use of case finding tests followed by more specific tests applied to defined borderline ranges (Britton *et al.*, 1975, Rhodes 1977); and the direct incorporation of clinical data specified on the request form in order to narrow down the need and selection of such tests. The application of such tactics in optimizing *in vivo* investigations is considerably advanced by the quantitation of image data so that objective decision aiding ranges can be developed to indicate the management alternatives.

THE THERMOGRAPHIC IMAGE

By E. F. J. Ring

Royal National Hospital for Rheumatic Diseases

An international committee set up four years ago by the European Thermographic Association (ETA) will shortly publish a report on terminology. Two of the sections will deal with the image and the processed image. Various terms are in use in each European language to describe the same image form, and translation can be hazardous. For example a simple greytone oscilloscope image has been referred to as black and white, continuous tone and monochrome. These terms are derived from photographic sources. Since a thermogram can be displayed to show a range of isotherms, colour is used to simplify presentation, and the word colour isothermogram is proposed. By standardization colour-coded isotherms can provide visual indication of temperature distribution. However, two differing colour sequences are used. One places red as maximal, and follows the basic spectral order. The other system places white at maximal temperature followed by yellow, then red, green and blues. Attempts to standardize these parameters and the terms used to describe the differing image forms are part of the current programme of the ETA.

REFERENCES

Britton, K. E., Quinn, V., Brown, B. L., and Elkins, R. P., 1975. A strategy for thyroid tests. *British Medical Journal*, *3*, 73–86.

Rhodes, B. A. (ed.) 1977. *Quality control in Nuclear Medicine*, pp. 73–86 (C. V. Mosby, St. Louis).

Book reviews

The mediastinum—radiologic correlations with anatomy and pathology. By E. Robert Heitzman, pp. xi+341, 595 illus., 1977. (C. V. Mosby, Saint Louis; distribution in UK, Henry Kimpton, London). £29·55.

This is a splendid book. It is a careful and comprehensive analysis of radiological signs associated with the mediastinum, particularly the various "lines" and "stripes" that have been so much in the literature in the last few years. A clear and readable text is supported by excellent illustrations and numerous references.

The foundation of the book is a careful analysis of the anatomical basis of the radiographic shadows demonstrated by a combined study of sagittal and coronal sections of cadavers and corresponding CT scans and conventional radiographs and tomograms. There is a wealth of important information here. It shows, I suspect, how much is commonly missed in routine reporting simply because we do not yet appreciate what we are overlooking.

Some examples of the sort of subsidiary themes that so greatly enhance the book are: the normal distribution of mediastinal fat and its increase in Cushing's syndrome, the course of the azygos vein crossing behind the lower end of the trachea, the recognition of which structure causes what shadow at the lung apex, the normal variability of the anterior and posterior junction lines, the changing shape of the cardiac incisura with respiration, and so on.

Occasional Americanisms lend charm to the text (*e.g.* "It is higher in back than it is in front") and prove it was not written by an Englishman!

This reviewer learned a lot on reading it and is going to read it again. Nearly everyone who reports on chest radiographs will want to do the same. Departmental libraries should certainly have a copy.

David H. Trapnell.

Ultrasonography in Obstetrics and Gynaecology. Edited by R. C. Sanders and A. E. James, Jr., pp. xii+425, illus., 1977 (New York, Appleton-Century-Crofts), £26·00.

The aim of this book is to place ultrasound in its clinical perspective as one of the many diagnostic tools which may help the clinician. Several of the 45 contributors to its 31 chapters have been successful in doing this, but on the whole the book does not achieve its aim.

Its partial failure is primarily due to its general structure. There are too many chapters and many of them concern diagnostic categories such as trophoblastic disease, rather than clinical problems like the management of threatened abortion.

Surely it is by now quite unnecessary to include a chapter on physics in such a book, and is it really essential to have 123 scans of fibroids in one chapter?

In contrast there is a short chapter on embryology which I found especially relevant and valuable, though I wished it could have been more comprehensive. In addition, the chapter discussing alternative techniques for placental imaging is very thorough and exemplifies the editors' aims. Conversely one is not surprised to read that one contributor finds the diagnosis of multiple pregnancy very difficult from ten to 14 weeks gestation when one sees the poor quality bi-stable images which illustrate his chapter. It would have been helpful if this, and several other contributors, had taken the opportunity to review the published literature on their subject.

The book would have been improved if the editors had pruned its contents by at least one third. There is, however, much useful information within this book and the good index will help the reader to locate it.

H. B. Meire.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

STATEMENT BY THE INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

After its meeting in Stockholm in May 1978, the ICRP issued a statement about its work and its basic recommendation. The Commission also issued a series of textual revisions to certain paragraphs in ICRP Publication 26. Copies of the statement and revisions can be obtained on application to Dr. F. D. Sowby, Scientific Secretary to ICRP, Clifton Avenue, Sutton, Surrey.

PRINCIPLES OF CLINICAL TRIALS IN CANCER

An evening meeting organized by The British Institute of Radiology to be held on October 19, 1978 at 32 Welbeck Street, London, W1.

Speakers: Mr. M. Baum, Dr. A. Tucker and Dr. K. D. MacRay.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

NUCLEAR MEDICINE IN PAEDIATRICS JOINT MEETING WITH THE BRITISH INSTITUTE OF RADIOLOGY AND THE ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

A one day meeting on Nuclear Medicine in Paediatrics will be held in Edinburgh on Friday, October 20, 1978.

One session will be devoted to renal disease, one to cardiac and respiratory disease and one to general topics. Dr. David Gilday will be reviewing the clinical application on nuclear medicine in children.

Proffered papers on any aspect of nuclear medicine in paediatrics are invited.

Detailed programme and registration forms available from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

RADIOBIOLOGY MEETINGS

The following meetings are scheduled at the Institute: "The scientific basis of radiation protection", October 20, 1978. "The combination of radiotherapy and chemotherapy", December 2, 1978. "Radiation chemists talk to biologists", January 19, 1979.

Further information can be obtained from the General Secretary, The British Institute of Radiology (01–935 6237).

UNIVERSITY OF OXFORD; ALAN NICHOLS MEMORIAL LECTURE

Dr. B. J. Shepstone, D.Phil., M.B., B.Ch., (D.Sc. Bloemfontein), M.D. (Cape Town), F.Inst.P., Senior Research Fellow, Wolfson College, Clinical Lecturer in Radiology, University of Oxford, will deliver the Ninth Lecture on Thursday, November 16, 1978 at 7 p.m. in the Witts Lecture Theatre, The Radcliffe Infirmary.

Subject: *Ultrasonics and its place in modern comparative radiology.*

CT AND ULTRASONIC SCANNING IN RADIOTHERAPY PLANNING

A joint meeting of The British Institute of Radiology and the Hospital Physicists Association, will be held on Thursday, November 16, 1978 at the Institute House, 32 Welbeck Street, London W1.

Information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

NMG IMAGING

An evening meeting organized jointly by The British Institute of Radiology, the Institution of Electrical Engineers and the Institution of Electronic and Radio Engineers, will be held on Thursday, November 16, 1978 at the Institute House, 32 Welbeck Street, London W1.

Information from the General Secretary, The British Institute of Radiology.

BRITISH MEDICAL ULTRASOUND SOCIETY ANNUAL MEETING AND EXHIBITION

To be held November 27–28, 1978 at the Civic Centre, Newcastle upon Tyne.

Further details from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

PROBLEMS OF BENIGN AND MALIGNANT BONE TUMOURS

A joint evening meeting organized by the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, to be held on Friday, January 19, 1979, at the Royal Society of Medicine, London.

Speakers: Dr. Mary Catto, Dr. P. Jacobs, Mr. D. R. Sweetnam and Dr. G. E. Flatman.

Further information: contact the Royal Society of Medicine.

NEW RADIOPHARMACEUTICALS INCLUDING ^{123}I

An all day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on Wednesday, February 14, 1979 at the Middlesex Hospital Medical School.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

IMAGING IN NUCLEAR MEDICINE

An evening meeting to be held on Thursday, February 15, 1979 at The British Institute of Radiology, 32 Welbeck Street, London, W1, organized jointly by The British Institute of Radiology, the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology).

Further information contact the General Secretary, The British Institute of Radiology.

WORKSHOP ON THE USE OF COMPUTERIZED TOMOGRAPHIC SCANNERS IN RADIOTHERAPY

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proffered papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

1979 THE BRITISH INSTITUTE OF RADIOLOGY ANNUAL CONGRESS

The 37th British Institute of Radiology Annual Congress and Scientific Exhibition will be held at the Middlesex Hospital Medical School on April 26–27, 1979. Included in a programme of invited papers on diagnostic, therapy, radiological physics and nuclear medicine topics will be the Presidential Address by Mr. W. M. Ross entitled *The Institute, yesterday and tomorrow*, and the Silvanus Thompson Memorial Lecture by Professor G. E. Adams, on *Past, present and future of hypoxic cell sensitizers*.

Details and registration from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. G. B. Schofield, Medical Officer, British Nuclear Fuels Ltd., on *Biological control in a plutonium production facility* at The British Institute of Radiology, 32 Welbeck Street, London, W1 on Thursday, May 17, 1979.

INTERNATIONAL SYMPOSIUM ON INTERVENTIONAL RADIOLOGY

An E.A.R. Symposium, organized by the Portuguese Society of Radiology and Nuclear Medicine, will be held May 30–June 2, 1979 in the Algarve, Portugal.

Proposed sessions include vascular therapy; selective embolization and management; catheter implantation in chemotherapy and percutaneous treatments; ultrasonic guiding techniques and nuclear imaging as a guiding technique for biopsy and fluid aspiration.

For further information contact the Portuguese Society of Radiology and Nuclear Medicine, 123, 1.° Esq., Avenida Elias Garcia, Lisbon 1, Portugal.

NUCLEAR CARDIOLOGY

A workshop organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on June 20, 1979 at the Institute House.

Further information contact the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The L. H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Book reviews

Obstetrical diagnosis by radiographic, ultrasonic and nuclear methods 770

Cardiac catheterization and angiocardiography 787

Radiation exposure from consumer products and miscellaneous 792

Medical Radionuclide Imaging 798

Understanding radiography 801

Planning and plutonium 801

Pediatric radiology 807

Advanced exercises in diagnostic radiology. No. 10: The urinary tract 813

Atlas of cardiovascular nuclear medicine 820

Introduction of nuclear radiation detectors 835

Traite de radiodiagnostic. Tome XIX. Radiopèdiatrie 835

The mediastinum-radiologic correlations with anatomy and pathology 840

Ultrasonography in obstetrics and gynaecology 840

Clinical and Experimental Applications of Krypton 81m

Edited by J. P. Lavender

British Journal of Radiology, Special Report 15,
This work is composed of papers presented at an International Meeting held in June 1977 concerned with a new physiological tool; the use of a very short-lived radioactive gas krypton 81m.
Krypton 81m is a noble gas with a 13 second half life available from a portable generator with a half life of 4½ hours. Although known for a number of years it has only been used with any frequency by physiologists and clinicians since 1975.
The first section of the book deals with the production of the parent isotope rubidium 81 and the design of generators. The second section comprises a series of papers concerned with the use of the equilibrium image as both a picture and a measure of regional lung ventilation and perfusion. It also outlines problems of deriving absolute values of lung function. In the third section, papers illustrate the use of krypton 81m as a clinical tool in the diagnosis of pulmonary embolic disease and other pulmonary diseases and compare such information with that obtained from the more familiar xenon 133. In the last section the use of intra-arterial krypton as a marker of regional myocardial and cerebral blood flow is discussed. This technique, which has been most highly developed in the case of the myocardium, allows detailed images of the myocardial perfusion to be recorded. Perhaps its clearest application is in following rapid changes of regional myocardial perfusion in response to transient ischaemia, stress and drugs.
The discussion following each paper allows an assessment of the value and place of this new technique.
ISBN 0 905749 01 4
ISSN 0306–2120 Price £12·00
Orders to:
Publications, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237) or through your bookseller.

VOL 51 NO 610 OCTOBER 1978

The British Journal of Radiology

Contents

Page

Editorial. A new home for The British Institute of Radiology. 755

Review article. The current role of cancer chemotherapy. 756
E. S. Newlands

Orbitocranial asymmetry 771
E. H. Burrows

Pseudopolyposis in Crohn's disease. 782
A. H. Freeman, F. R. Berridge, A. P. Dick, J. A. Gleeson and R. Zeegen

Hepatic oil embolism following lymphography. 788
H. Ngan and K. W. James

Volume changes in the rat renal cortex during urography. 793
V. Hegedüs, P. Faarup, T. Nørgaard and C. Lønholdt

Contrast media during coronary arteriography: electrocardiographic changes in the presence of normal coronary arteries. 799
M. Kyriakidis, G. Jackson and D. Jewitt

Isotope renography and long-term follow-up of renal transplant patients. 802
C. C. Doherty, J. F. Douglas and Mary G. McGeown

The tolerance of mouse tails to necrosis after repeated irradiation with X rays 808
J. H. Hendry

Iridium-192 afterloaded implant in the retreatment of head and neck cancers. 814
A. M. Nisar Syed, B. H. Feder, F. W. George III and D. Neblett

Technical notes. 821
Positioning errors in bone mineral measurement.
M. I. Al Jarallah, J. A. Archer-Hall and P. E. Francois
"Floppy" into "flippy"—or two for the price of one.
L. G. Brock
New grey tone rapid process films for ultrasound imaging.
W. A. Copland, S. R. Wild and W. N. McDicken

Case reports. 825
Diagnosis of an ileal duplication with sodium pertechnetate ^{99}Tc^{m}.
N. W. Garvie, G. S. M. Harrison and D. M. Ackery
Chronic oesophageal stricture due to moniliasis.
F. M. Kelvin, W. M. Clark, W. M. Thompson and T. Hauch
Inverted Meckel's diverticulum as a cause of anaemia and continuing blood loss.
J. L. Boldero
A radiographically documented intra-utirne femoral fracture.
E. E. Christensen and G. W. Dietz

Short communication. 832
The effect of vitamin E on cellular survival after X irradiation of lymphoma cells.
K. Fonck and A. W. T. Konings

Education in, and status of, radiology in Europe. 834

Correspondence. 836
Absorbed radiation dose in radiation synovectomy.
C. S. Bowring and D. H. Keeling
Radiation protection in dentistry.
P. N. Hirschmann
CAT stimulation of retina.
S. Cochrane Shanks

Proceedings of The British Institute of Radiology. 838
The theory and practice of data display (February 13, 1978).

Forthcoming events and other notices. 841

Book reviews. Inside back cover

Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0007-1285
12603

13.4.79

November 1978

THE BRITISH JOURNAL OF RADIOLOGY

X-ray diagnosis
Radiation oncology
Nuclear medicine
Ultrasound
Radiological physics
Radiobiology
Radiation protection
and related disciplines

Published by
The British Institute of Radiology

The British Journal of Radiology

FOUNDED 1896

The Editorial Committee consists of:

The Editors:

D. K. BEWLEY, M.A., PH.D. F. STARER, F.R.C.P., F.R.C.R.

The Deputy Editors:

B. T. HALE, M.B., CH.B., F.R.C.R., D.M.R.T. N. W. RAMSEY, PH.D., F.INST.P.

J. ROYLANCE, F.R.C.R.

and

The Associate Editors:

A. B. AYERS, M.D., D.M.R.D., F.R.C.R.
THELMA D. BATES, M.B., CH.B., F.R.C.R., D.C.R.A.
D. COSGROVE, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. COTTRALL, B.A., M.SC., PH.D., F.INST.P.
R. DICK, M.B., B.S., M.R.A.C.R., F.R.C.R.
C. D. R. FLOWER, M.A., F.R.C.P.(C), F.R.C.R.
N. E. GILLIES, B.SC., PH.D.
J. A. GLEESON, M.B., F.R.C.P., F.R.C.R., D.M.R.D.
H. GRAVELLE, B.SC., M.B., CH.B., F.R.C.P.(E.), F.R.C.R., D.M.R.D.
J. L. HAYBITTLE, M.A., PH.D.
C. R. HILL, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. KEELING, M.A., M.SC., M.B.
I. KELSEY FRY, D.M., F.R.C.P., F.R.C.R.
B. KENDALL, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. MEIRE, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. PATTON, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. SCOTT, M.D.
T. SHERWOOD, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. VEALL, D.SC., F.INST.P.

The Associate Editors Overseas are:

P. ARMSTRONG, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
B. J. CREMIN, F.R.A.C.R., F.R.C.R. (South Africa)
J. R. CUNNINGHAM, M.SC., PH.D. (Canada)
H. A. LUKE, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. SIM, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. STANFORD, M.A., F.INST.P. (Australia)

Managing Editor: MRS. LEE SURRY

Communications should be addressed to the Editors in accordance with the Instructions to Authors which are published in the January issue of the Journal in each year and copies of which may be obtained on application to the Managing Editor.

ADVERTISEMENTS: Communications regarding accounts should be addressed to the Institute. All other communications should be addressed to Miss Hilary Cook, Advertising Manager, The British Journal of Radiology, Advertisement Department, 24a Litchfield Street, London WC2H 9NX.

SUBSCRIPTIONS: All communications should be sent to The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England. Notification of change of address should include an old mailing label and the new address. Claims for missing copies can only be allowed if received within two months of normal delivery date.

ANNUAL SUBSCRIPTION: (post free, payable in advance) £40·00 per annum (monthly) (U.S.A. $80). Single copies: £4·00.

Second class postage paid at New York. Mailing agents: N.Y. Expediters of the Printed Word Ltd., 527 Madison Avenue, Suite 1217, New York, N.Y. 10022, U.S.A.

The British Institute of Radiology

Incorporated by Royal Charter
Founded 1897

32 WELBECK STREET, LONDON W1M 7PG
Telephone: 01–935 6237 and 01–935 6867. Cable Address: "Britology, London W.1."

President: W. M. ROSS, T.D., D.L., M.D., F.R.C.S., F.R.C.R.

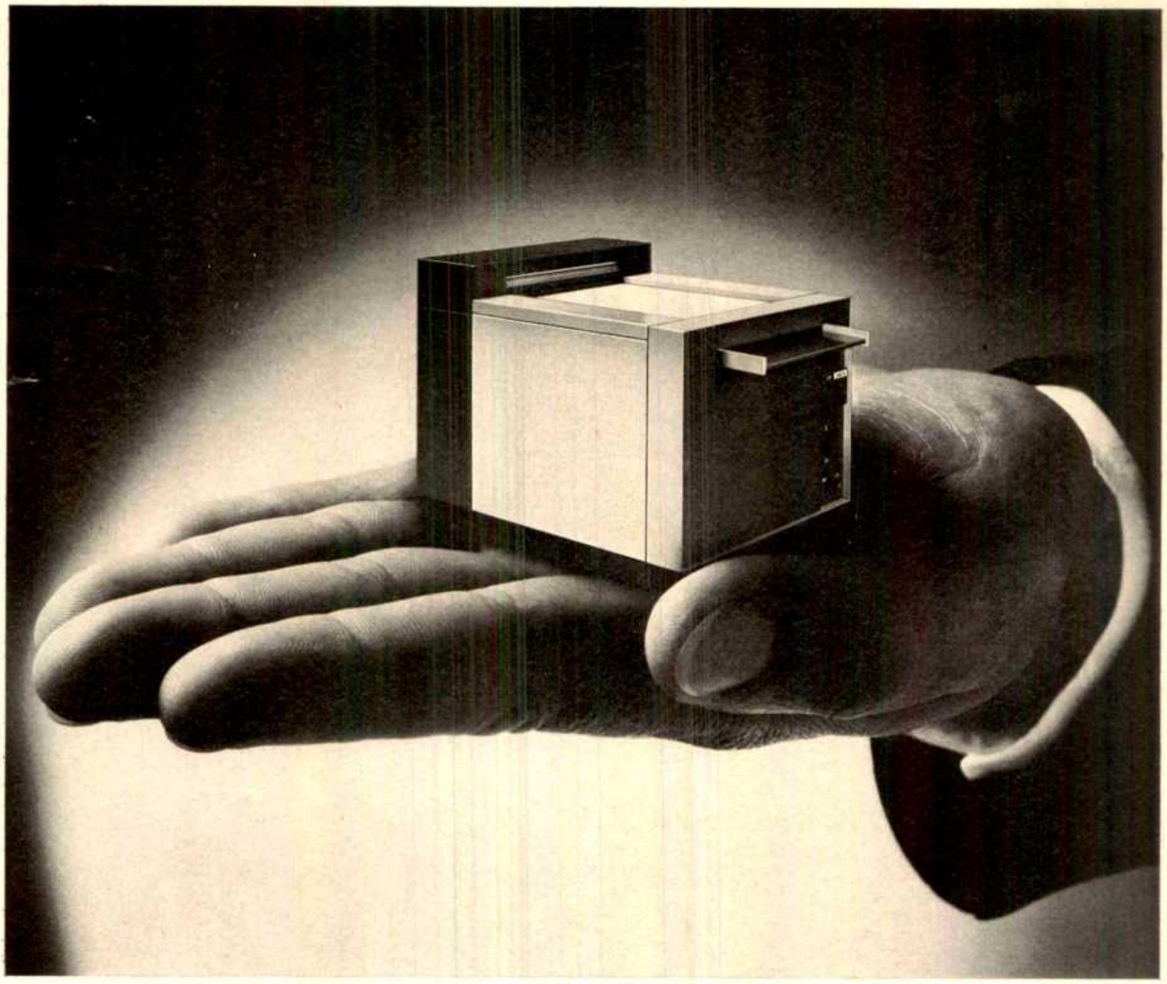
Hon. Secretaries:

W. HATELY, M.B., CH.B., F.R.C.P.E., F.R.C.R., D.M.R.D. S. B. FIELD, B.SC., PH.D.

Hon. Treasurer: D. T. KERRISK

THE BRITISH INSTITUTE OF RADIOLOGY is an association of persons interested in Radiology and allied subjects. Meetings are held monthly from October until May. Particulars of membership and other information may be obtained on application to the General Secretary at the Institute.

© British Institute of Radiology, 1978



The new CRONEX* T6 cuts x-ray film processing down to size.

High capacity x-ray film processing from a compact machine: that's the T6.

The CRONEX* T6 offers you the throughput you expect from far bigger processors and at a much lower cost. Easy to install and highly reliable, it is efficient and takes only 115 seconds for processing. In one hour you can process 175 35 x 43 cm films or 250 mixed sizes. The processor is compatible with the Du Pont Daylight System. Handles all CRONEX* medical x-ray films and is a perfect partner for our new CRONEX* automatic chemical mixer.

The T6 is silent when on stand-by and uses minimal amounts of electricity and water thanks to sophisticated solid state automatic controls with built-in logic.

The processor is designed to be installed in either conventional darkrooms or the most modern dispersed film handling areas, where its features permit a pleasant environment for staff and patients.

In addition, Du Pont's enthusiastic, experienced team of equipment service representatives stand behind all CRONEX* equipment: with fiendly advice on layout planning, smooth installation, scheduled maintenance programmes and emergency assistance should it be required.

Save space. Save time. Save money. The T6 is one processor that really cuts film processing down to size. To find out more about the new CRONEX* T6, write to the address below.

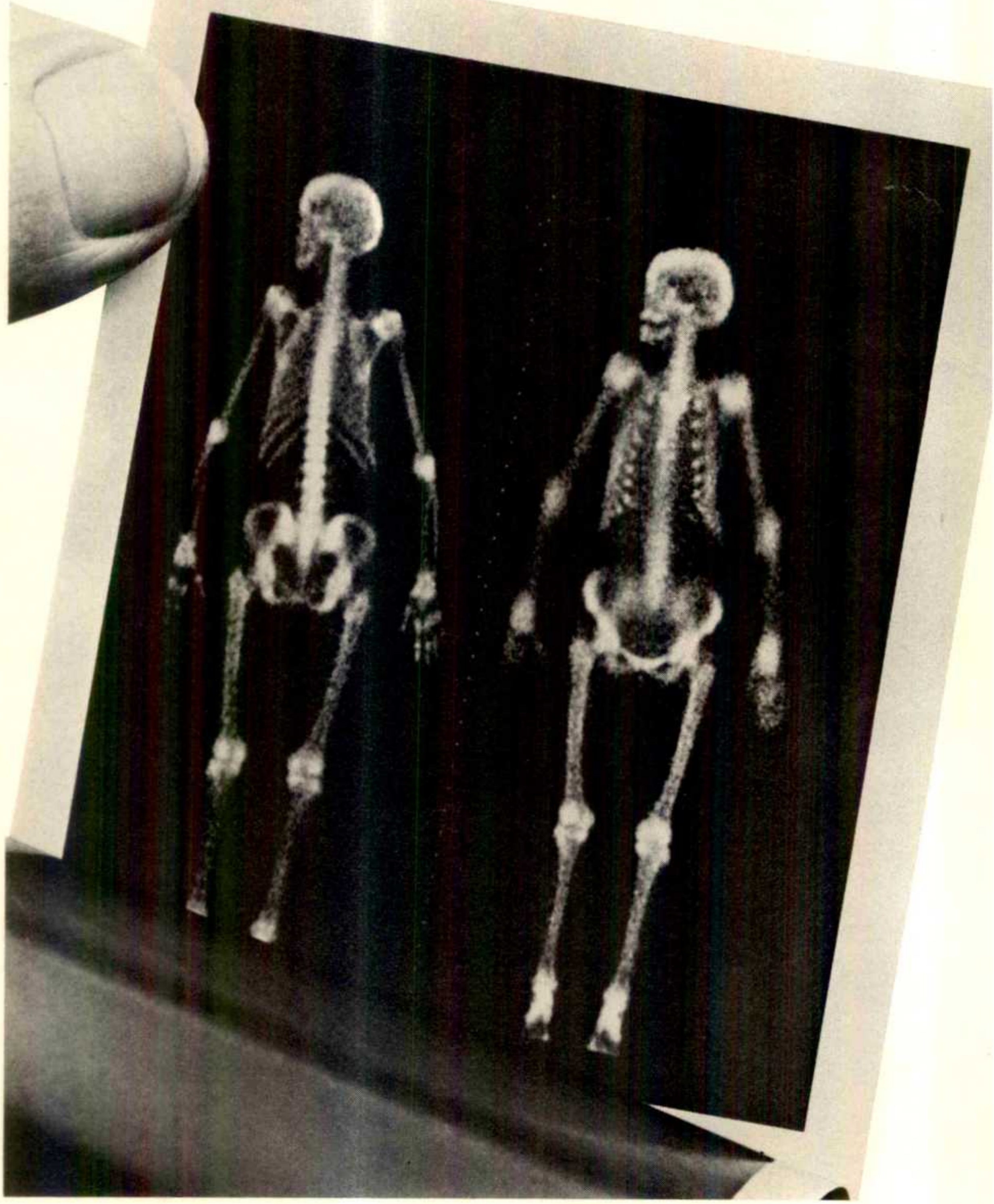
CRONEX* T6. THE SMALL PROCESSOR WITH THE BIG CAPACITY.

DU PONT

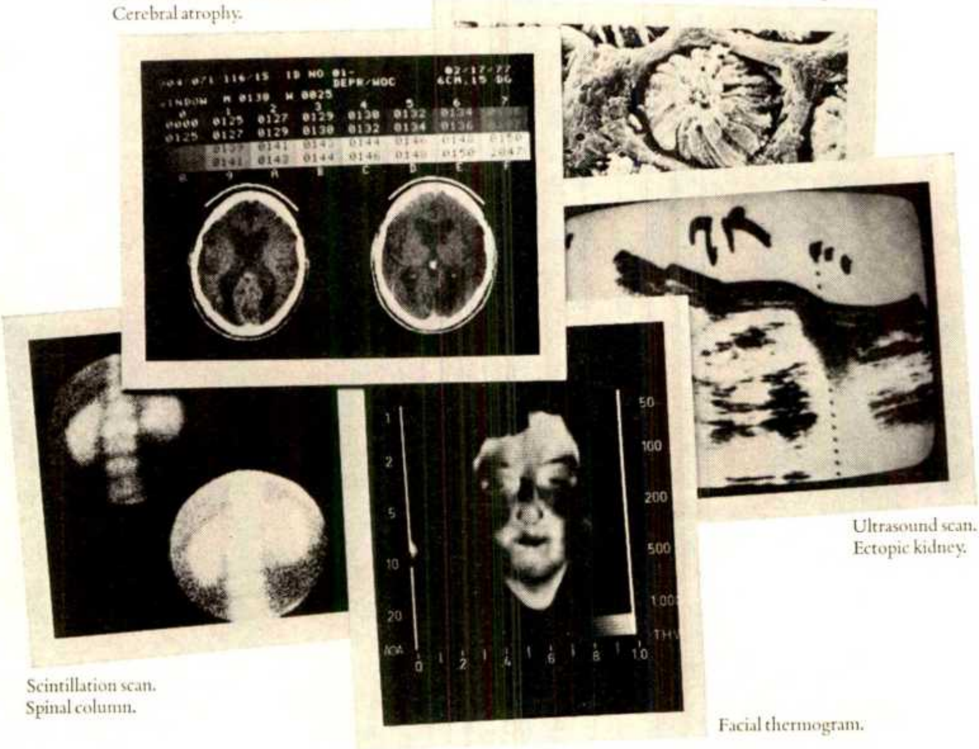
Du Pont de Nemours U. K. International – Photo Products Department – Hawkesden Road, St. Neots, Huntington, Cambridgeshire PE19 1QS
Tel.: (0480) 75341/(01) 2355286-88 Telex: 32159. *Du Ponts trademark

COLLEGE
LIBRARY

WE'LL HELP YOU GI



THE INSIDE STORY.



CT scan. Cross-section of brain. Cerebral atrophy.

Scintillation scan. Disease of joints.

Ultrasound scan. Ectopic kidney.

Scintillation scan. Spinal column.

Facial thermogram.

INSTANTLY.

We want you to get all the details possible in your iagnostic pictures.

That's why we have a technical assistance service. We'd like to help you take full advantage of the quality e've built into all our professional instant films.

And since the picture can't be better than the mage on your video monitor, our experts are prepared to elp you achieve optimum results from your particular iagnostic equipment.

Polaroid black and white Land films have the ensitivity, resolution, exposure latitude and grey scale apability necessary to give you excellent diagnostic hotographs on the spot. One of our films will give you oth a positive and a negative instantly. With our Polacolor 2 film you can record high-resolution colour images in 60 seconds. All of our films are self-developing. You don't need a darkroom or processing equipment to get the pictures you want.

These films are being used in computerised tomography, ultrasound imaging, nuclear medicine and thermography. If you're working in any of these fields, make our technical assistance service part of your diagnostic system. It costs you nothing.

For more information or a demonstration, phone Ray Taylor on Freefone 2143 or write to Polaroid (U.K.) Ltd., Business and Professional Products Division, Ashley Road, St. Albans, Herts., AL1 5PR.

We can't help you diagnose your patients' troubles, but we can certainly help you diagnose your photography.

POLAROID

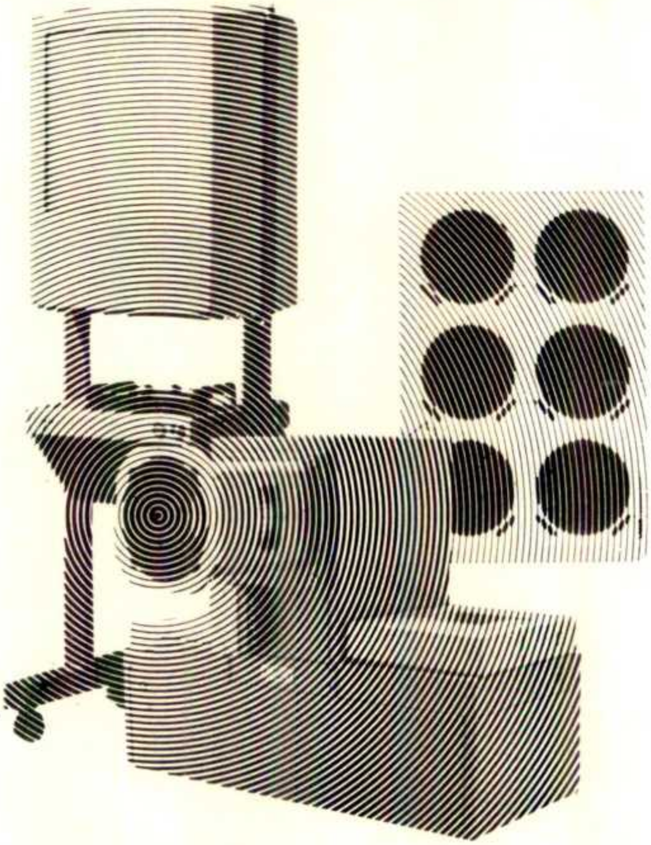
INSTANT FILMS FOR CRT RECORDING

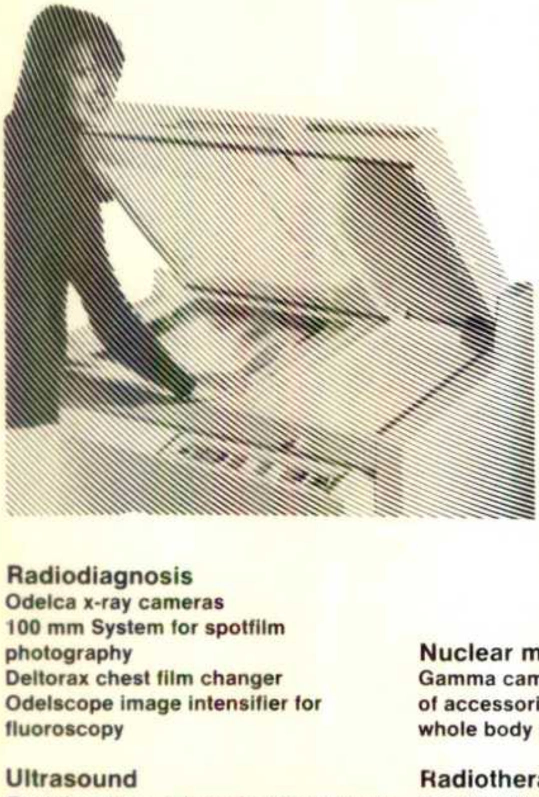
'Polaroid' and 'Polacolor' are registered trademarks of Polaroid Corporation, Cambridge, Mass., U.S.A.
Polaroid (U.K.) Ltd., Ashley Road, St. Albans, Herts. ©Polaroid Corporation 1978

40 years of experience and expert knowledge can be made yours very easily

Oldelft

Oldelft England Ltd
16 Barclay Road, Croydon CRO 1JN
Tel. (01) 681 1171, telex 946154





The Anodica image intensifier camera, Helio viewer, Cadrix viewing frame and Delcomat copier shown here are part of the **Oldelft 100 mm sheetfilm system for spotfilm photography** which covers every single procedure in the handling of x-ray films: **exposure, processing, viewing, copying, framing, filing.** Each piece of equipment can be purchased singly and fitted into existing routines.

Radiodiagnosis
Odelca x-ray cameras
100 mm System for spotfilm photography
Deltorax chest film changer
Odelscope image intensifier for fluoroscopy

Ultrasound
Real time linear phased array systems
Cardiac phased array sector scanners
General purpose gray-scale compound scanners

Nuclear medicine
Gamma cameras with complete range of accessories (e.g. multi-imager, whole body scanning bed)

Radiotherapy
4 and 15 MeV linear accelerators
Cobalt units

Radiotherapy planning
Simulix-Y simulator with Simtomix accessory for analog whole body tomography

Pulmonary function testing
Computerized equipment for the pulmonary lab
Automated procedures in spirometry, flow/volume loop analysis and exercise testing

---

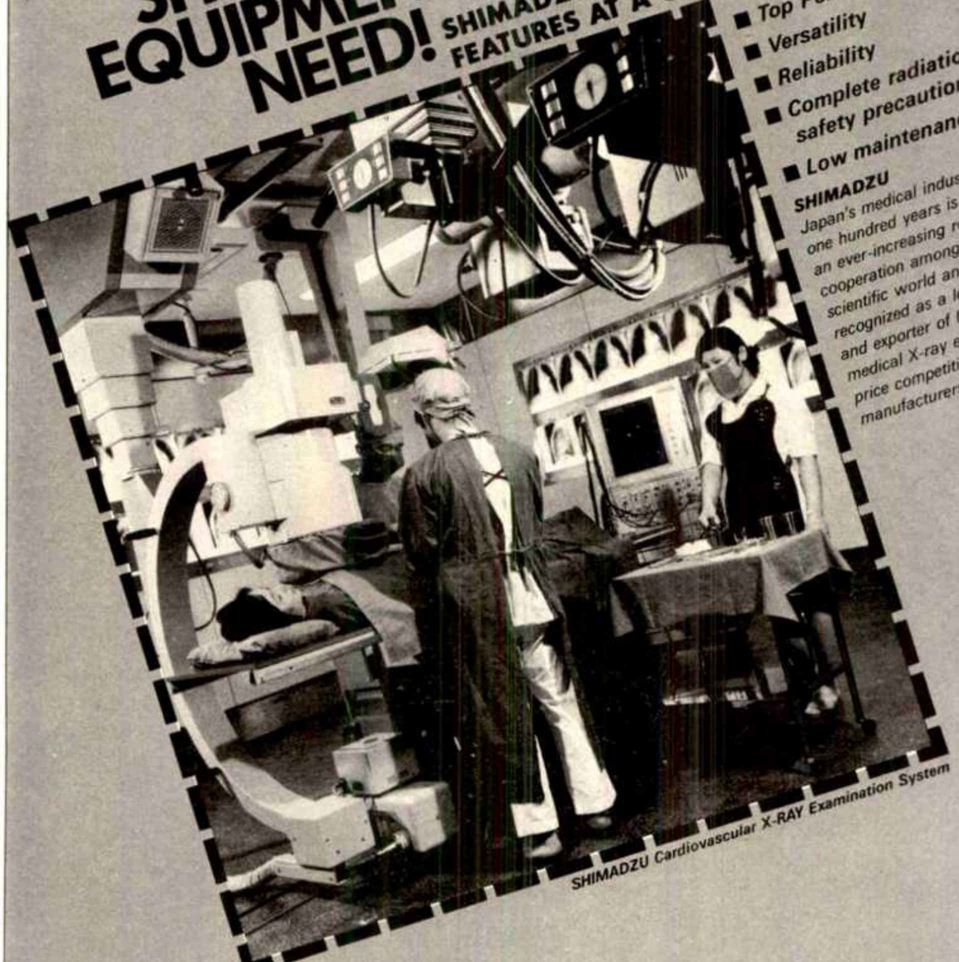
Head Office: Holland. (nv Optische Industrie De Oude Delft). 2612 xe Delft, Postbox 72, Tel. (015) 13 29 23/12 40 44, Telex 32 384,
België/Belgique 2100 Deurne, Twee Gezusterslaan 34, Tel. (031) 24 93 05,
Deutschland D 6300 Giessen/Lahn, Postfach 5420, Tel. (0641) 4 10 49,
España Madrid 16, Uruguay 13, Tel. (01) 259 1698,
France 91403 Orsay, B.P. 86, Tel. (01) 907 5900,
Italia 00146 Roma, Via della Vasca Navale 84, Tel. (06) 55 84 311,
Japan Osaka, Postbox 1042, Tel. (06) 309 09 61,
Sverige 17206 Sundbyberg 6, Postbox 670, Tel. (08) 98 38 95,
Schweiz 8618 Oetwil am See, Zelglistrasse 5, Tel. (01) 92 91 318,
USA Fairfax, Virginia 22030, 2735 Dorr Avenue, Tel. (703) 573 7020

A ROOM FULL OF SHIMADZU X-RAY EQUIPMENT IS ALL YOU NEED!

SHIMADZU X-RAY EQUIPMENT OFFERS ALL THESE FEATURES AT A COMPETITIVE PRICE

- Top Performance
- Versatility
- Reliability
- Complete radiation safety precautions
- Low maintenance cost

SHIMADZU
Japan's medical industry pioneer for one hundred years is continuing to play an ever-increasing role in international cooperation amongst the leaders of the scientific world and is internationally recognized as a leading manufacturer and exporter of highly sophisticated medical X-ray equipment at a price competitive with all leading manufacturers.



SHIMADZU Cardiovascular X-RAY Examination System

SHIMADZU
SEISAKUSHO LTD. KYOTO JAPAN
INTERNATIONAL MARKETING DIV.
14-5, Uchikanda 1-chome Chiyoda-ku, Tokyo Japan Phone: Tokyo 03-296-2352
Overseas Telex: No.0222-4275 SHMDT J Cable Address: SHIMADZU TOKYO

SHIMADZU MID-EAST SCIENTIFIC OFFICE
Flat No. 10, 16 Mahmud Azmi Street Zamalek, Cairo
Arab Republic of Egypt(P.O. Box: Zamalek P.O. Box 32, Cairo)
Phone: 804375 Cable Address: MIDSHIMAZU, CAIRO

THORACIC MYELOGRAPHY

AMIPAQUE MEANS SAFETY

- excellent tolerance, especially with regard to epileptogenic effects.
- adhesive arachnoiditis unlikely to occur.

The excellent tolerance of AMIPAQUE has been confirmed in more than 150 000 examinations covering the various parts of the subarachnoid space.

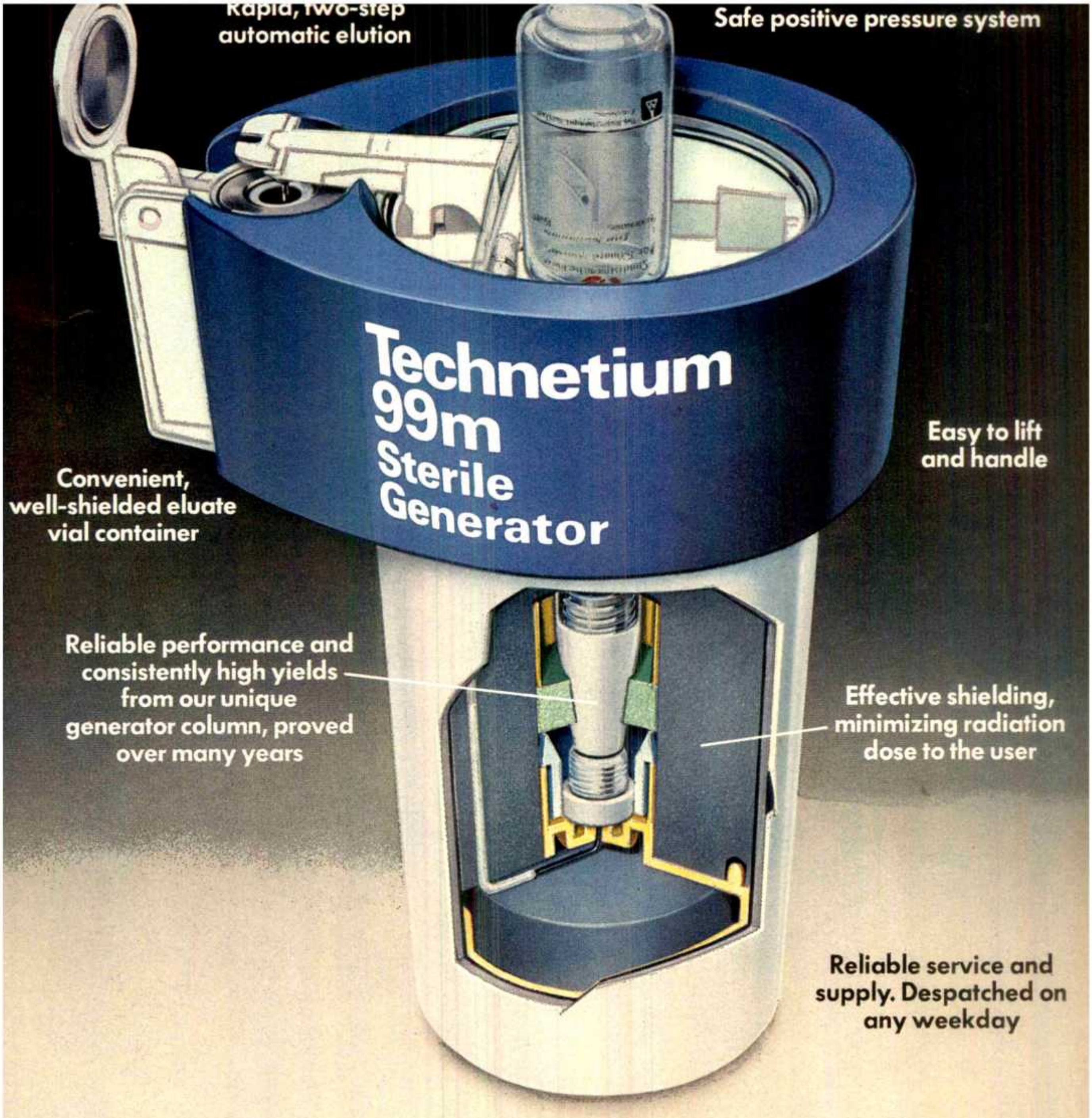
In thoracic myelography AMIPAQUE – metrizamide – offers better demonstration of small structures and narrow spaces, because of its miscibility with the CSF and low viscosity.

AMIPAQUE is completely eliminated from the body.

AMIPAQUE is the only water-soluble contrast medium which can safely be used in thoracic myelography.

NYEGAARD·OSLO
P.O. Box 4220 Torshov, Oslo 4, Norway.

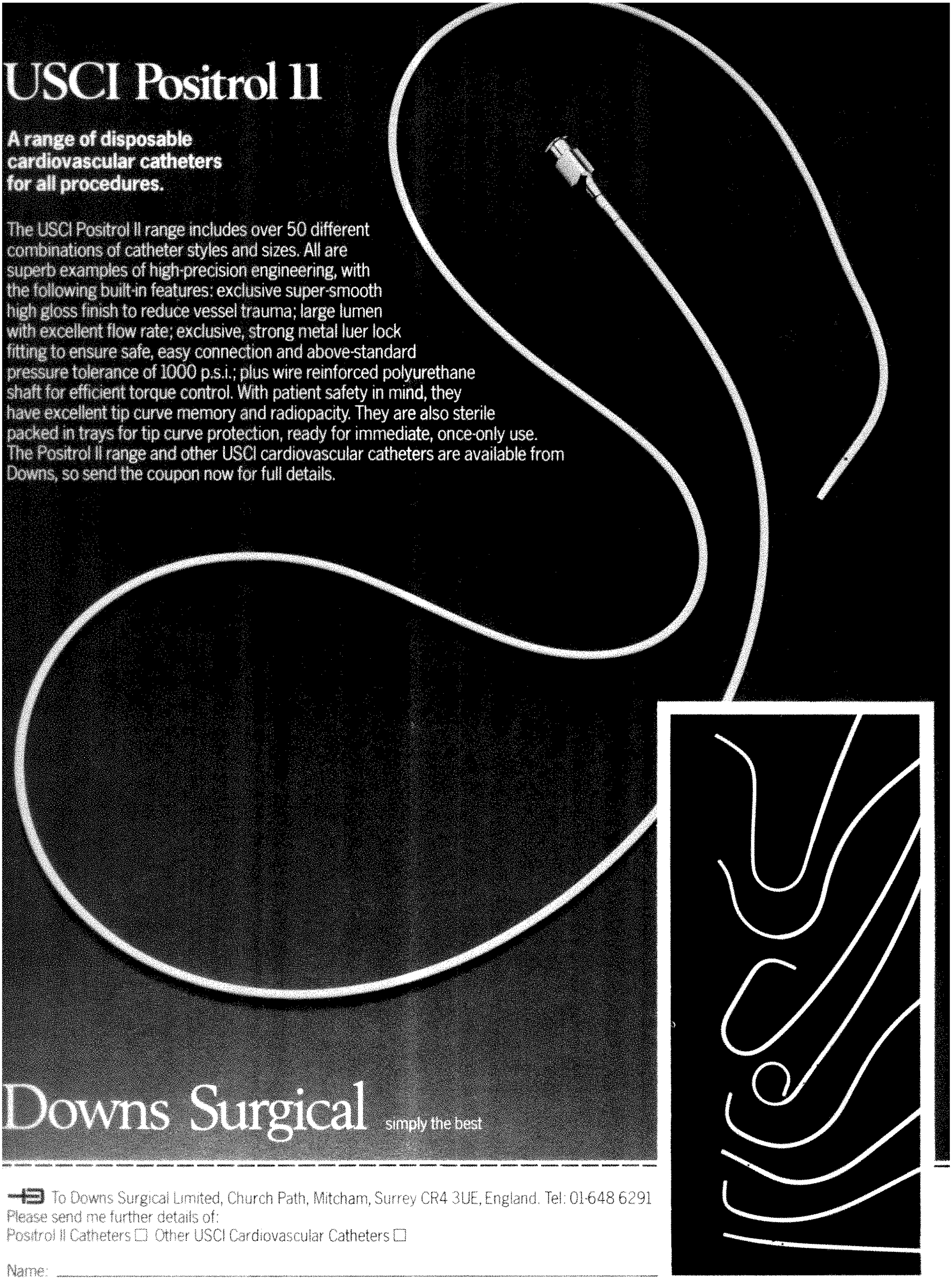
Amipaque


Rapid, two-step automatic elution
Safe positive pressure system
Technetium 99m Sterile Generator
Easy to lift and handle
Convenient, well-shielded eluate vial container
Reliable performance and consistently high yields from our unique generator column, proved over many years
Effective shielding, minimizing radiation dose to the user
Reliable service and supply. Despatched on any weekday

Introducing our second generation generator

The Radiochemical Centre Amersham

The Radiochemical Centre Limited, Amersham, England. Tel: Little Chalfont (024 04) 4444
In West Germany: Amersham Buchler GmbH & Co KG, Braunschweig. Tel: 05307-4693-97



USCI Positrol II

A range of disposable cardiovascular catheters for all procedures.

The USCI Positrol II range includes over 50 different combinations of catheter styles and sizes. All are superb examples of high-precision engineering, with the following built-in features: exclusive super-smooth high gloss finish to reduce vessel trauma; large lumen with excellent flow rate; exclusive, strong metal luer lock fitting to ensure safe, easy connection and above-standard pressure tolerance of 1000 p.s.i.; plus wire reinforced polyurethane shaft for efficient torque control. With patient safety in mind, they have excellent tip curve memory and radiopacity. They are also sterile packed in trays for tip curve protection, ready for immediate, once-only use. The Positrol II range and other USCI cardiovascular catheters are available from Downs, so send the coupon now for full details.

Downs Surgical simply the best

To Downs Surgical Limited, Church Path, Mitcham, Surrey CR4 3UE, England. Tel: 01-648 6291
Please send me further details of:
Positrol II Catheters ☐ Other USCI Cardiovascular Catheters ☐

Name: ______________________________

Address: ______________________________

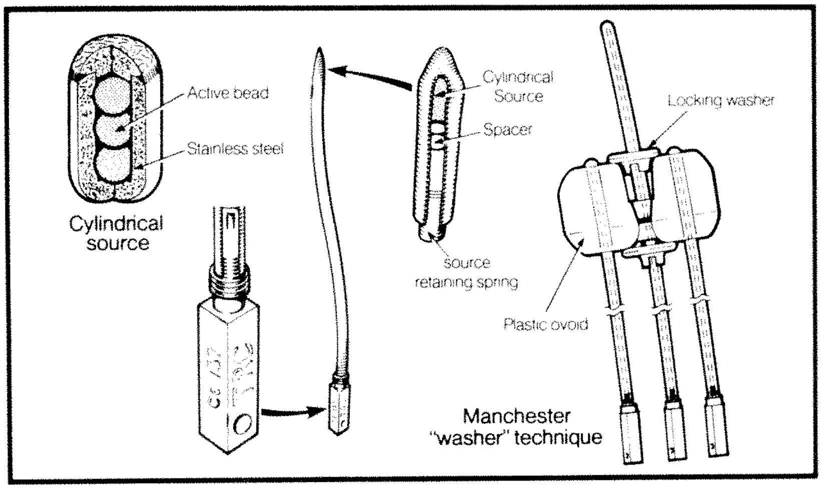
Our Afterloading Systems put brachytherapy right on target

With the addition of our new caesium-137 gynaecological afterloading system, we now supply a comprehensive range of products for intracavitary and interstitial radiotherapy.

Intracavitary radiotherapy

Our caesium-137 "Manchester" afterloading system consists of X-Ray opaque PVC applicators which allow the "washer," "spacer" or "tandem" techniques to be used. The guide tubes are flexible and have a diameter of only 6.3 mm overall. Complete kits are supplied sterilized in packaging designed for maximum convenience in use.

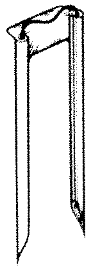
The sources contain glass beads in welded stainless steel capsules assembled into flexible source trains for which special shielded containers are supplied. Iso-dose curves are available for each source train. Individual sources and source trains are also supplied for most of the currently available remote afterloading systems.



Interstitial radiotherapy

Our iridium-192 flexible wire afterloading systems include complete sets of applicators and accessories for the Pierquin/Paine technique. All accessories for these systems are pre-packed ready for use and sterilized where necessary. Platinum clad iridium-192 wire in 500 mm lengths is readily available in activities up to approximately 0.3 mCi/mm providing exposure rates of up to 0.16 mR per hour at 1 metre.

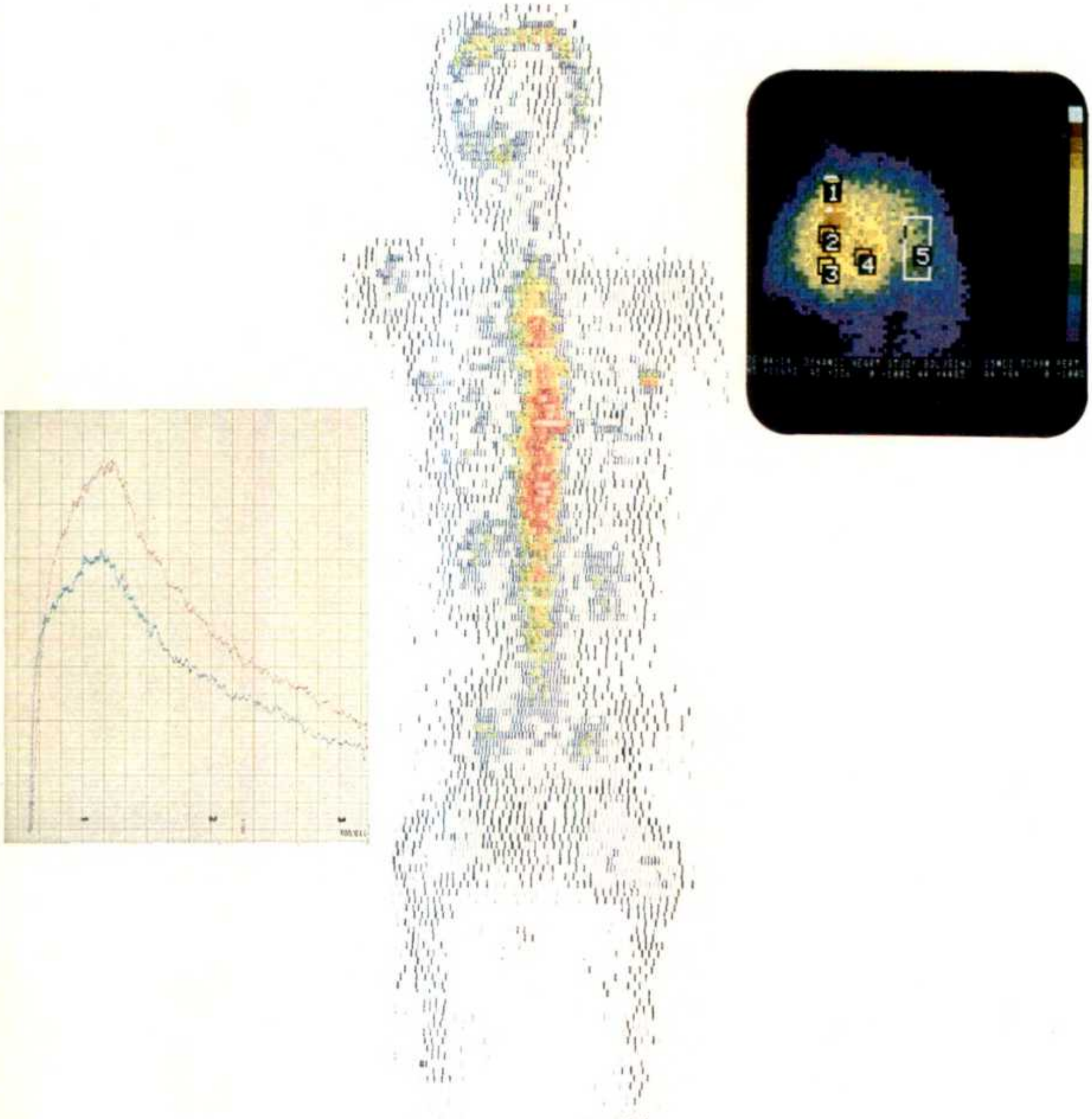
Iridium-192 "hairpins" and single pins: Thicker platinum coated iridium-192 wire is supplied pre-shaped as "hairpins" and single pins for use with slotted guide needles which are made in stainless steel to the designs of Pierquin and Paine.



The Radiochemical Centre
Amersham

Full information is available on request.
The Radiochemical Centre Limited, Amersham, England. Telephone: 024-04-4444
In the Americas: Amersham Corporation, Illinois 60005. Telephone: 312-593-6300
In W. Germany: Amersham Buchler GmbH & Co KG, Braunschweig. Telephone: 05307-4691
1885

Overall evidence



Medical Systems

This total body scan, dynamic heart study and kidney function, contribute only part of the overall evidence of Philips total capability in nuclear medicine. For in addition to developing, manufacturing and supplying the specialised equipment, we provide a complete range of services to back it all up.

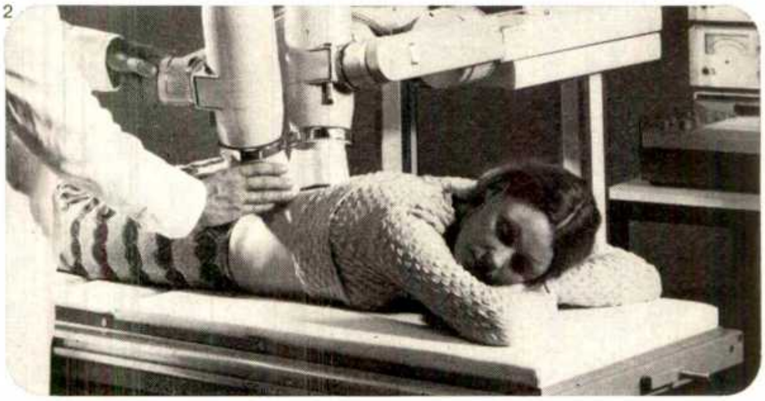
Expert guidance in the organisation and layout of your nuclear medicine department; objective advice about the most appropriate equipment to use; information on protective measures in line with general regulations.

Once decisions are made, we will install and commission the equipment and instruct you and your staff on its use. And if ever breakdowns do occur, we've an international network of specialised technicians who are always on call.

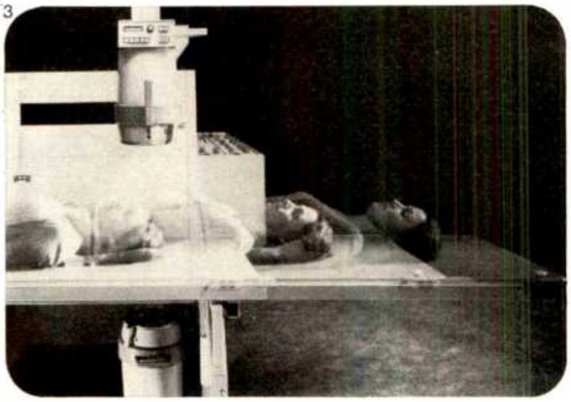
The whole programme is based on intensive medical-electronic research and extensive knowledge and experience in the field of medical diagnostics. That's the overall evidence Philips offer for progress in nuclear medicine.

1

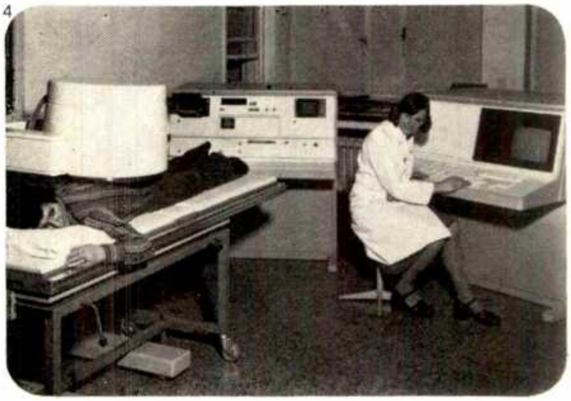
2



3



4



The range of equipment in Philips Nuclear Medicine Programme include a **Microcuriemeter** for rapid calibration of prepared radio-pharmaceuticals prior to patient administration, as well as **Automatic Sample Changers** (photo 1 shows the 100 sample version).

The sample changers form part of an integrated series of Function Measuring instruments comprising **Counter/Timers** (with optional printer control and background subtraction), a **Gamma Analyser** combining Isotope Selector, Pulse height Analyser, H.T. supply and Ratemeter, and single and dual-channel **Chart Recorders.** There is a choice of single or dual-channel systems - Renography for example (photo 2) - plus a **Lead Castle** for measurement in-vitro.

Total body scanning (photo 3) is an optional feature of the Philips **Universal Scintillation Scanner.** Based on modular design principles, it can be supplied in a variety of configurations from a basic single detector scanner to a dual-channel installation offering facilities for photo-scan, profile scanning and 4-track compact-cassette recording and playback.

The **Gamma Camera** (photo 4, left) features a selection of collimators for a wide variety of applications, and an output for connection of peripherals such as a data **Processing and Display System** (photo 4, right). Designed specifically to provide rapid quantitative and qualitative diagnostic information, Philips PDS employs a mini computer with disc-operated software programs. A FORTRAN option extends system capability. There is no specialised knowledge of data processing techniques required for program execution.

COUPON

If you would like further evidence on our nuclear medicine program, complete this coupon and send to:
Philips Industries, Medical Systems Division, Building QM, Room 326,
Eindhoven, The Netherlands.

Company: __________

Name/Position: __________

City/Country: __________

Street/P.O. Box: __________

PHILIPS

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd
45 Nightingale Lane London SW12 8SX

University of London
Royal Postgraduate Medical School

FAST NEUTRON THERAPY

9–12 April 1979

Three similar courses have been organised by the Royal Postgraduate Medical School and the Medical Research Council Cyclotron Unit, Hammersmith Hospital, and have been found to be particularly valuable to doctors interested in treating patients with high LET radiation and, in particular, for those who have already started fast neutron programmes or will start them in the near future.

The fourth course will be held from 9 to 12 April 1979 and will consist of:

Lectures and discussions on the physical, biological and clinical effects of 7.5 MeV neutrons. Clinical effects on tumours and normal structures will be compared with those produced by photons.

The demonstration of patients treated with fast neutrons during the past nine years.

Practical demonstrations and explanations of the special techniques which have been evolved.

Demonstrations and treatment of patients actually receiving neutron radiation at the time of the course.

Throughout the four days of the course, members of the Fast Neutron Clinic, radiobiologists, physicists, engineers and the MRC isotope staff will be available for discussion with the participants.

Because of the emphasis on the demonstration of patients the number of clinical participants must be restricted to a maximum of fourteen. In addition, ten physicists could be included for lectures and demonstrations, excluding the clinical demonstrations.

Course organiser: Dr. Mary Catterall

Course fee: £100 (full course, including catering)
£80 (excluding clinical demonstrations, including catering)

Application forms may be obtained from:
The School Office (SSC)
Royal Postgraduate Medical School
Hammersmith Hospital
Du Cane Road, London W12 0HS
Telephone: 01–743 2030 ext 351

Closing date for applications: 1 February 1979

WANTED

Used telecobalt, rotating isocenteric machine with a head capacity not less than 3000 curie. Machine in good order.

Please reply Box No 13 The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

1 AOT ELEMA–SCHONANDER
Film Changer 12″ × 10″

for disposal at Southampton General Hospital.
Further information available from
District Superintendent Radiographer–
Southampton 771257.

Written offers to District Supplies Officer,
30/32 Tremona Road, Southampton.

Radiologist

South West
London/Surrey
Area

required to look after a small but very active NDT Department which includes radiography, dye penetrant, ultrasonic and pressure testing. Experience in the radiography and general non-destructive testing of welded components would be a considerable advantage but applicants experienced in other fields will be considered. Ministry approval and experience with Ministry/Aerospace requirements would also be an advantage.

Salary circa £5,500 plus bonus scheme.

Replies to Box No 14 The British Journal
of Radiology, 32 Welbeck Street,
London W1M 7PG.

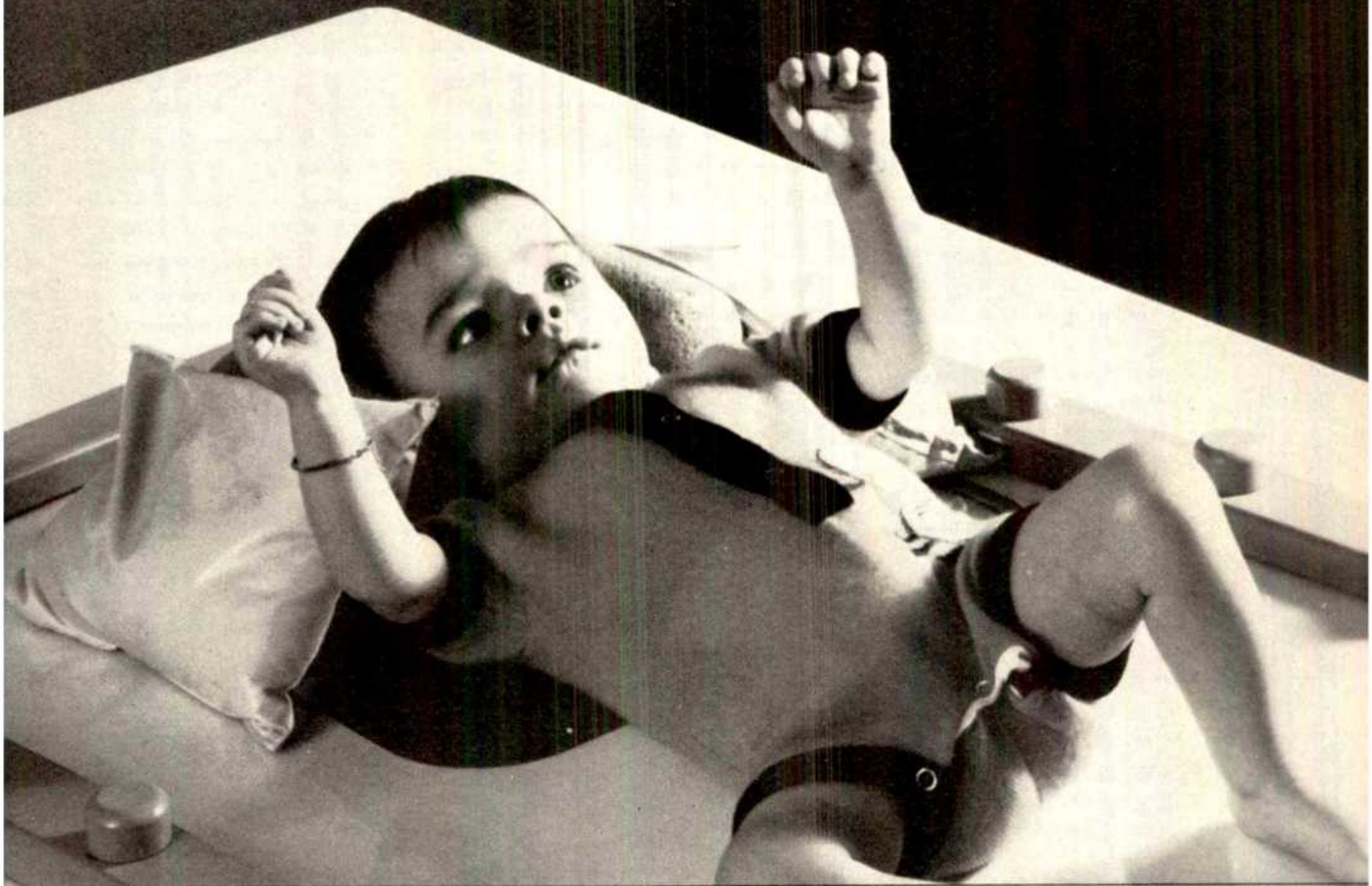
Paediatric radiography without tears

The Junior DIAGNOST system for paediatric radiography consists of three dedicated units, each designed for a specific application: Junior DIAGNOST V, Junior DIAGNOST H, Junior DIAGNOST T.

The Junior DIAGNOST V provides speed and efficiency in chest examinations of babies and young children, while the Junior DIAGNOST H ensures accurate, effortless positioning of even the most recalcitrant infant. The third unit in the system, the Junior DIAGNOST T, is a truly practical paediatric tomograph: positive but comfortable immobilization, combined with very short exposure times, provides valuable diagnostic information.

In spite of its outstanding performance, the Junior DIAGNOST system is not confined to the well-endowed paediatric hospital.

A shared X-ray tube and generator, together with minimum space requirements, make the system a sound economic investment for every X-ray department confronted with small but awkward patients.



PHILIPS

PHILIPS Medical

Most CT scanners have a past.

Ours has a future.

With the advent of the CT scanner, a bewildering variety of systems were rushed onto the market - while the technique itself was still in a state of rapid development. As a consequence, some systems were outdated even before installation was completed.

Now, after careful study of the clinical requirements, close consultation with the medical profession, and long and rigorous testing, Philips present the TOMOSCAN 300: a state-of-the-art CT scanner designed first and foremost as a medical instrument.

Developed and produced by a reliable manufacturer of medical equipment with years of experience in X-ray diagnostics, the TOMOSCAN 300 is the medically-oriented system that meets all requirements for routine clinical practice. It features scan times as short as two and a half seconds, and offers geometrical enlargement for outstanding image quality in a variety of applications - whole-body, cerebral, and paediatric.

PHILIPS

PETERSON F R
PET100320-205
BD 20 MAR 16 M
ED 02 SEP 77
4287
NR 5 SP 40
TH 12 MM
ANG 0
KV 120 MA 250
FOV 40 CM
PHILIPS TOMOSCAN 300
+100
WW 100
WL +50
+0
QUALITY JOY HOSPITAL
The CT scanner with a future.
PHILIPS
Medic
Syste

Now, Colocode enables you to control your X-Rays as precisely as you may wish.

Whether your Filing System is large or small; numeric, alphabetic, or a mixture of the two; you can visibly index new or existing X-Rays so as to;

- **Restrict or eliminate misfiling**
- **Speed-up sorting**
- **Speed file recognition**
- **Faster weeding for transfer to in-active storage, or destruction**
- **Fitted on the top of the envelope in drawer-type filing**
- **Fitted on the side of the envelope in shelf filing**
- **Directly on the film to indicate examination**

Colocode is a systems range of pure vinyl self-adhesive labels of high quality in fifteen vivid colours available from shelf-stock in a variety of presentations numbered, lettered and plain.

COLOCODE

WARDRAY THE X-RAY PROTECTION EXPERTS

WARDRAY PRODUCTS (CLERKENWELL) LTD.
15/19 BAKERS ROW, LONDON EC1R 3DT. 01-837 2666/8

free university amsterdam

The **Faculty of Medicine** invites applications for the position of a

physician in nuclear medicine

in the department of Nuclear Medicine (head: dr. G.A.K. Heidendal) of the University Hospital (Academisch Ziekenhuis der Vrije Universiteit).

The department offers exposure to all aspects of nuclear medicine, including in vivo imaging, function studies and in vitro studies. There are opportunities for conducting research.

Additional information can be obtained from dr. G.A.K. Heidendal M.D., phone 020 - 548 48 11.

Candidates are expected to agree with the christian charter of the Free University.

Those who want to apply are requested to write to the
Personnel Department, P.O. Box 7161, 1007 MC Amsterdam,
quoting reference number 223 - 2088.
The Free University is situated at the
De Boelelaan 1105, Amsterdam-Buitenveldert.

VU

Precise localization and simulation for any megavolt therapy unit

The Philips localizer/simulator can match precisely the settings of any type of megavoltage therapy machine from the smallest cobalt unit operating at 60 cm to the largest linear accelerators or betatrons with source to isocentre distances up to 130 cm.

The conflict, common to all simulators, between image size and free movement has been solved in the Philips unit by using a relatively small image intensifier arranged to scan an area of 59 cm square - larger than the biggest stationary intensifier can cover. Moreover, since the image intensifier weighs much less than a large stationary intensifier the gantry can be of lighter construction, without loss of accuracy. In fact the superb mechanical engineering ensures isocentric accuracy of ±1 mm. If you have a Cobalt 60, Betatron or linear accelerator - install a Philips Localizer/Simulator and experience inprovement in treatment preparation.

PHILIPS

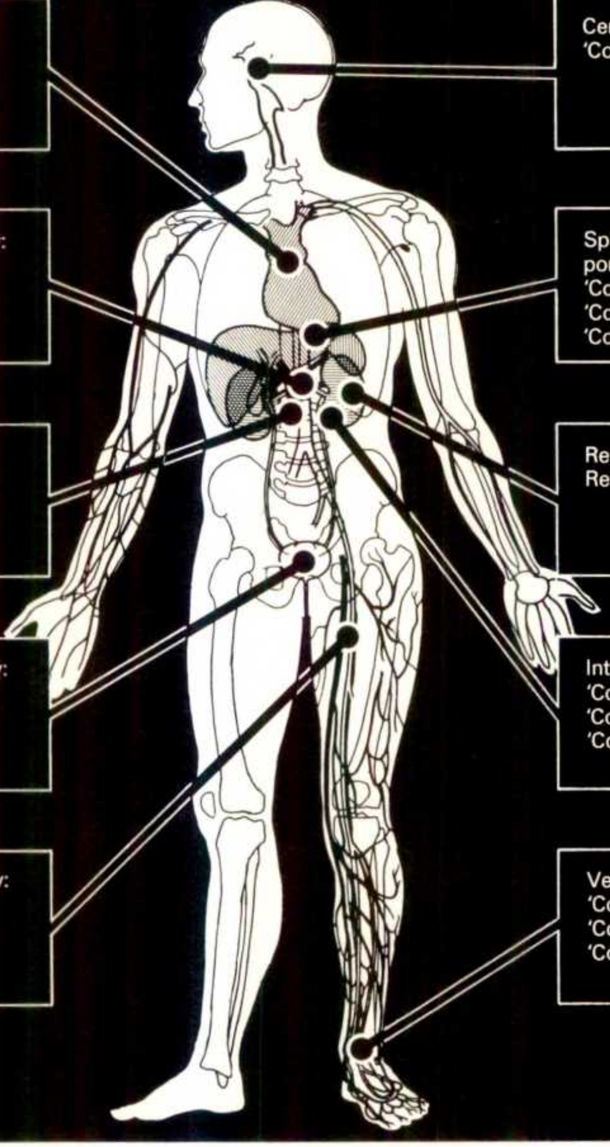
N.V. Philips' Gloeilampenfabrieken
PCP/Medical Systems Division
Building QM, Eindhoven, The Netherlands

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd.
45 Nightingale Lane, London SW12 8SX

PHILIPS

Medical Systems

The 'CONRAY' range of contrast media puts your patient fully in the picture



Angio-cardiography:
Cardio – 'Conray':
'Conray 420':
'Conray 280'

Abdominal-aortography:
'Conray 280':
'Conray 420':
'Conray 325':
Cardio – 'Conray'

Gastroenterography:
Gastro – 'Conray'

Retrograde cystography:
'Conray 280':
'Conray 420'
(suitably diluted)

Peripheral arteriography:
'Conray 280'

Cerebral angiography:
'Conray 280'

Splenography and
portal venography:
'Conray 280':
'Conray 420':
'Conray 325'

Retrograde pyelography:
Retro – 'Conray'

Intravenous urography:
'Conray 325':
'Conray 420':
'Conray 280'

Venography:
'Conray 280':
'Conray 420':
'Conray 325'

Conray Contrast Media

There is a wide variety of formulations and almost certainly one to meet your specific requirements however exacting they may be.

'Conray'* contrast media are formulations of meglumine iothalamate, sodium iothalamate or combinations of the two.

Full information supplied on request to
May & Baker Ltd Dagenham Essex RM10 7XS
*trade mark of Mallinckrodt Inc.

M&B May&Baker

A member of the Rhône-Poulenc Group of Companies

MA 6535

Dyanne has designs on growing old gracefully.

Dyanne is a clinical data processor for recording manipulating and interpreting static and dynamic studies produced by gamma cameras.

Simplicity of operation is the keynote for everyday use. Data is presented in a clean easy-to-read form and the user may 'access' the raw data whenever required.

Dyanne may be as interactive or as automatic as needs dictate, thus providing an unparalleled level of interaction between the user, computer and gamma camera.

Dyanne has been designed to meet the needs of an expanding technological discipline. Our software will allow you to initiate your own routines and incorporate new procedures through the use of simple protocols.

You can up-date with ease, and this means that you can extend Dyannes' processing capabilities way beyond the limits of less flexible systems.

We're convinced that as soon as you use this powerful data processor it will mark the beginning of a long and industrious relationship. With this in mind we've made sure that in the exciting world of nuclear medicine Dyannes data processing capabilities won't suddenly let you down with an obsolescent bump.

LINK SYSTEMS

Halifax Road, High Wycombe,
Bucks. HP12 3SE, England.
Tel: 0494 24145 Telex: 837542

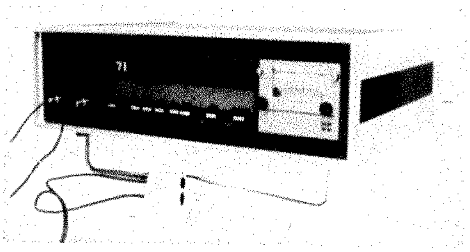
Worldwide sales and service

DIGITAL ECHOENCEPHALOGRAPHS

(MANUFACTURED BY RADIONICS MEDICAL DIVISION OF CANADA)

digiecho 1000

- portable, battery operated
- requires no previous experience
- digital measurement of midline
- competitively priced



digiecho 2000

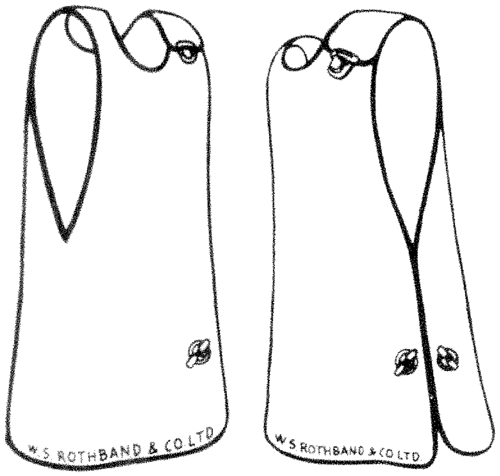
- rapid measurement rate
- selectable number of readings
- microprocessor controlled
- automatic printed record

DIAGNOSTIC SONAR LTD

1 Grange Road, Houstoun Industrial Estate, Livingston EH54 5DE, Scotland, U.K.
Tel. Livingston (STD Code 0589) 35165/6. Cable address: Sonar Livingston. Telex: 72591 DSONAR

DOCTOR "C" TYPE DOUBLE-SIDED APRON

Right side closed, left side has push-in-clip shoulder fastening, (or if "Velcro" preferred, please state on order).


W S ROTHBAND & CO LTD
W S ROTHBAND & CO LTD

Super-flexible–Multi-layered.

Foam padded shoulders.

Standard size is 24 in (61 cm) wide. Ladies slim fitting 21 in (53 cm) also available.

Lengths, choice of 33 in (84 cm), 36 in (91 cm), 39 in (99 cm), 42 in (107 cm).

Washable PVC colours, choice of royal blue, white, green, yellow, red.

Lead equivalents, choice of 0.25 mm, 0.35 mm, 0.50 mm.

This Apron has been specially designed by our Company for operators who stand "right-side-on" and who require protection without a gap on the right hand side.

W. S. ROTHBAND & CO. LTD
Telephone 061–834 1303

21 Elizabeth Street
Manchester M8 8WT, England

Established 1860

A new intensifier tube for neutron radiography

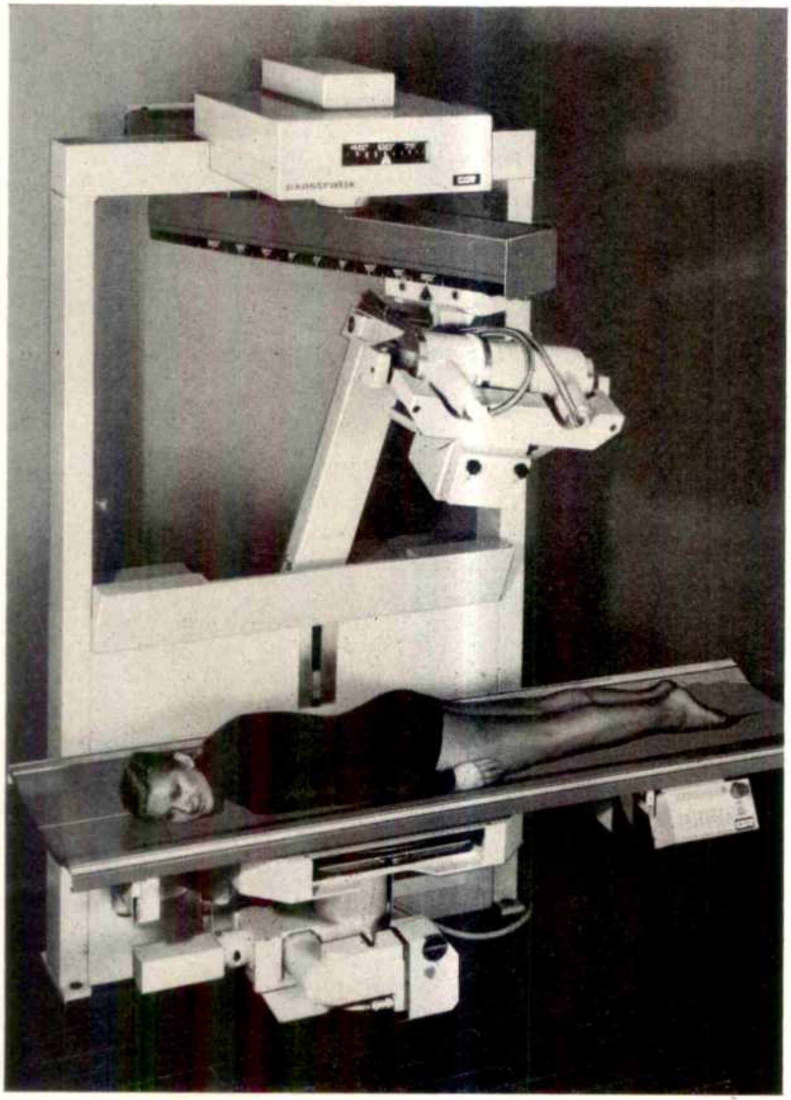
Exploiting the technological expertise acquired with its 4th generation of X-ray image intensifiers, THOMSON-CSF has developed a new image intensifier tube for radiography with thermal neutrons (about 0.3 eV). This tube, which has a 16-cm useful input field, permits obtaining real-time neutron radiographs of objects that cannot be detected with X-rays. Known as the THX 1410, it gives excellent image contrast and resolution and, if used with a television camera and monitor, it permits displaying the images in remote locations, video tape recording, and cine-recording. Any conventional video-signal processing technique can be used. These new tubes can be supplied complete with protective housings and integral HV power supplies.

THOMSON-CSF

THOMSON-CSF COMPONENTS AND MATERIALS LTD / RINGWAY HOUSE / BELL ROAD / BASINGSTOKE RG24 OQG / TEL. : (0256) 29155 / TELEX : 858865

3470

A precision unit with high quality image for complex tomography



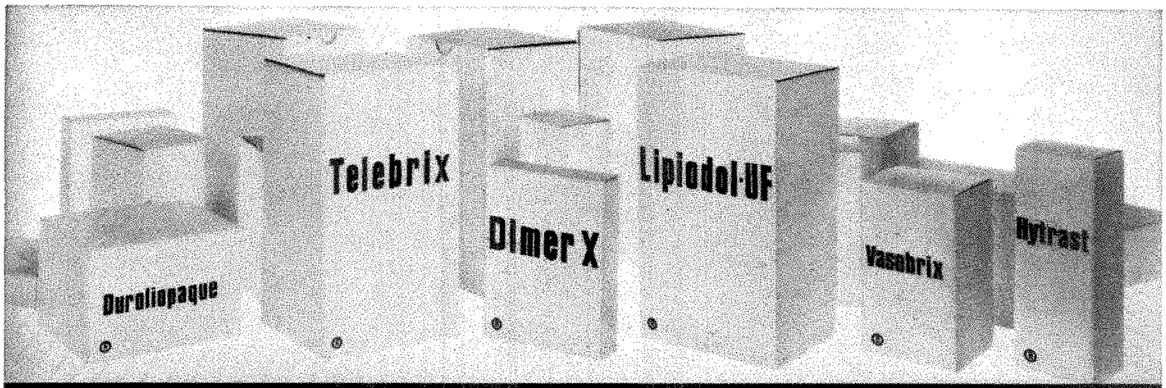
This compact and rigid self-contained unit for precision tomography linear in any direction, circular movents and zonography. The angle of swing and exposure time are determined by press-button from the control desk once the direction has been selected.

Complete Bucky examinations are simplified. The Exastratix allows double oblique angulations.

The Exastratix can be equipped with an image intensifier for TV flouroscopy.

Full details
and specifications from
CGR
MEDICAL LIMITED
Astronaut House, Feltham,
Middx. Tel: 01-890 8766.

EXASTRATIX
from
CGR



WE MANUFACTURE
contrast
MEDIA
OUR
products
ARE
known
WORLD-WIDE
OUR
name isn't
GUERBET
BETTER CONTRAST MEDIA THROUGH RESEARCH

Laboratoire Guerbet, 16/24, rue Jean-Chaptal
93601 AULNAY-SOUS-BOIS Cedex - FRANCE
Telex : Guerbet 690682

A High Performance Neutron Therapy System Based On Actual Clinical Experience.

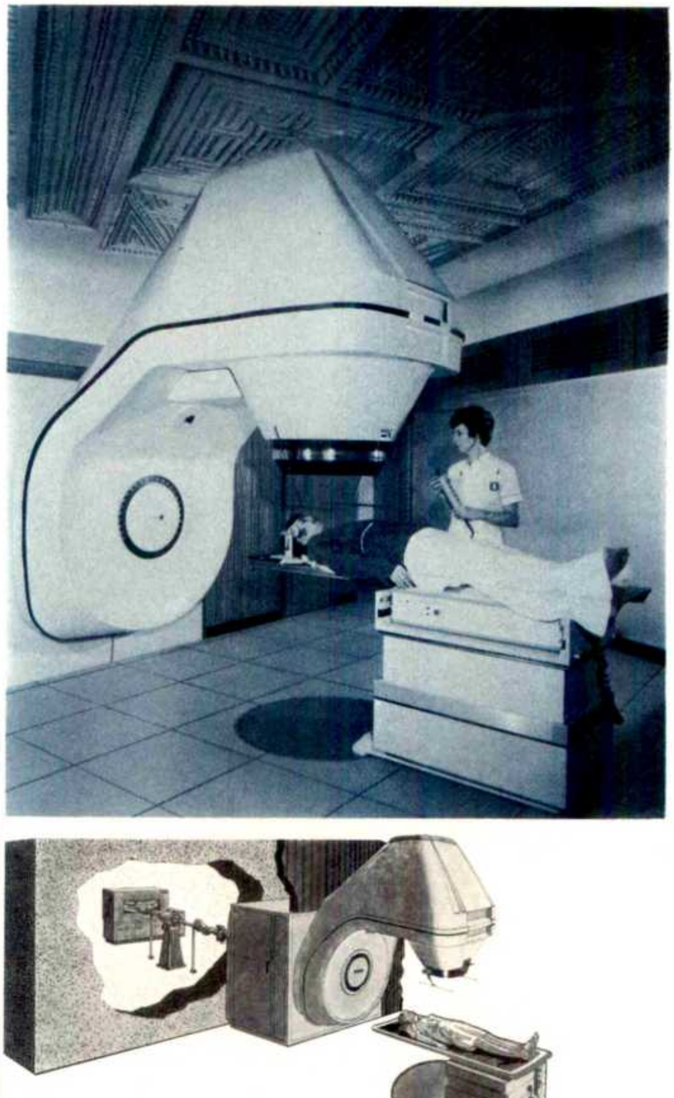
With performance comparable to the latest medical linear accelerators, the Model "CP" 42, our most powerful neutron therapy system, combines a relatively small cyclotron, producing fast neutrons via the proton on beryllium reaction, and an isocentric neutron therapy unit. The entire system can be housed in an area 6.6 m (22 ft.) wide by 16.4 m (54 ft.) long by 4.3 m (14 ft.) high.

The design of the cyclotron component in the system is based on more than twenty machines of its type built by our firm, which are currently in use all over the world. The machines have proved their reliability—several are operated routinely over 100 hours per week.

The isocentric neutron therapy unit has been tested successfully at Western General Hospital, Edinburgh, Scotland (pictured) and at Universitätsklinikum, Essen, West Germany.

The selling price of the "CP" Series system is generally comparable with that of high energy accelerators for photon and electron therapy.

We would be pleased to send you our complete brochure.



PERFORMANCE DATA FOR THE NEW MODEL "CP" 42 SYSTEM (a)

	(42 MeV P on thick Be) No Filter	Filter (b)
Dose Rate in Air (Rad/Min) (c) Guaranteed performance	84.0	50.0
Depth for 1/2 dose at maximum (g/cm²) (c) (d)	12.3	14.4

Notes:

(a) For therapists willing to accept a lower depth for 1/2 dose and lower dose rate, the Model "CP" 30 is available.

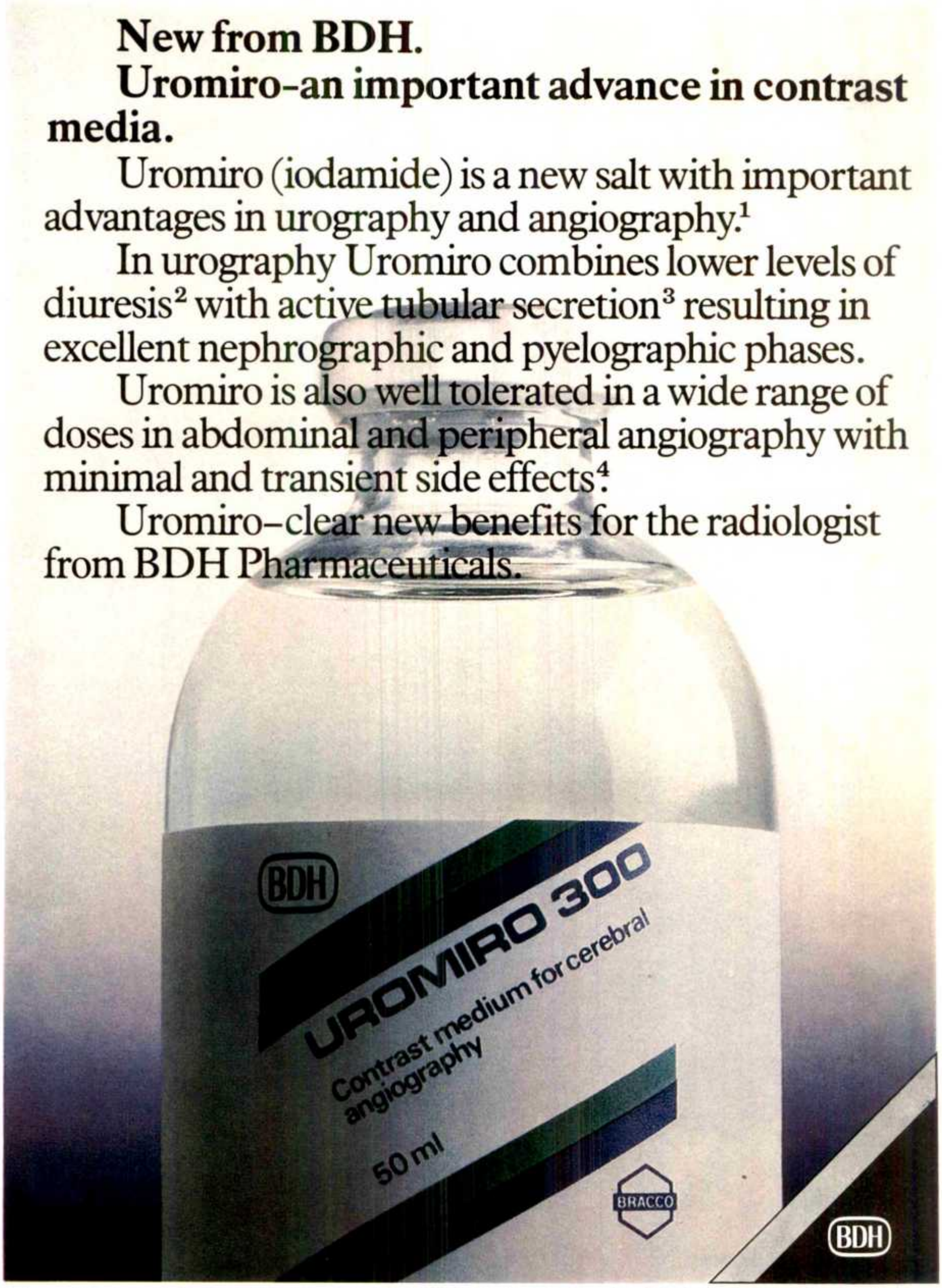
(b) Filter is 6 cm. polyethylene.

(c) $n + \gamma$, 10 cm. x 10 cm. field at 125 cm. SSD.

(d) Depth for maximum dose (g/cm^2), depth for 90% of maximum dose (g/cm^2), entrance dose % of dose at maximum build-up, and gamma component in air were measured for 35 MeV protons on thick Be target. The results with and without filter respectively were as follows: 0.82 and 0.60; 0.2 and 0.2; 43.0 and 40.0; 13.5% and 8.9%.

THE
CYCLOTRON
CORPORATION

950 Gilman St., Berkeley, California 94710, U.S.A.
Cable "Cyclotron Berkeley," Tel. (415) 524-8670, Telex 910-366-7116



New from BDH.

Uromiro-an important advance in contrast media.

Uromiro (iodamide) is a new salt with important advantages in urography and angiography.[1]

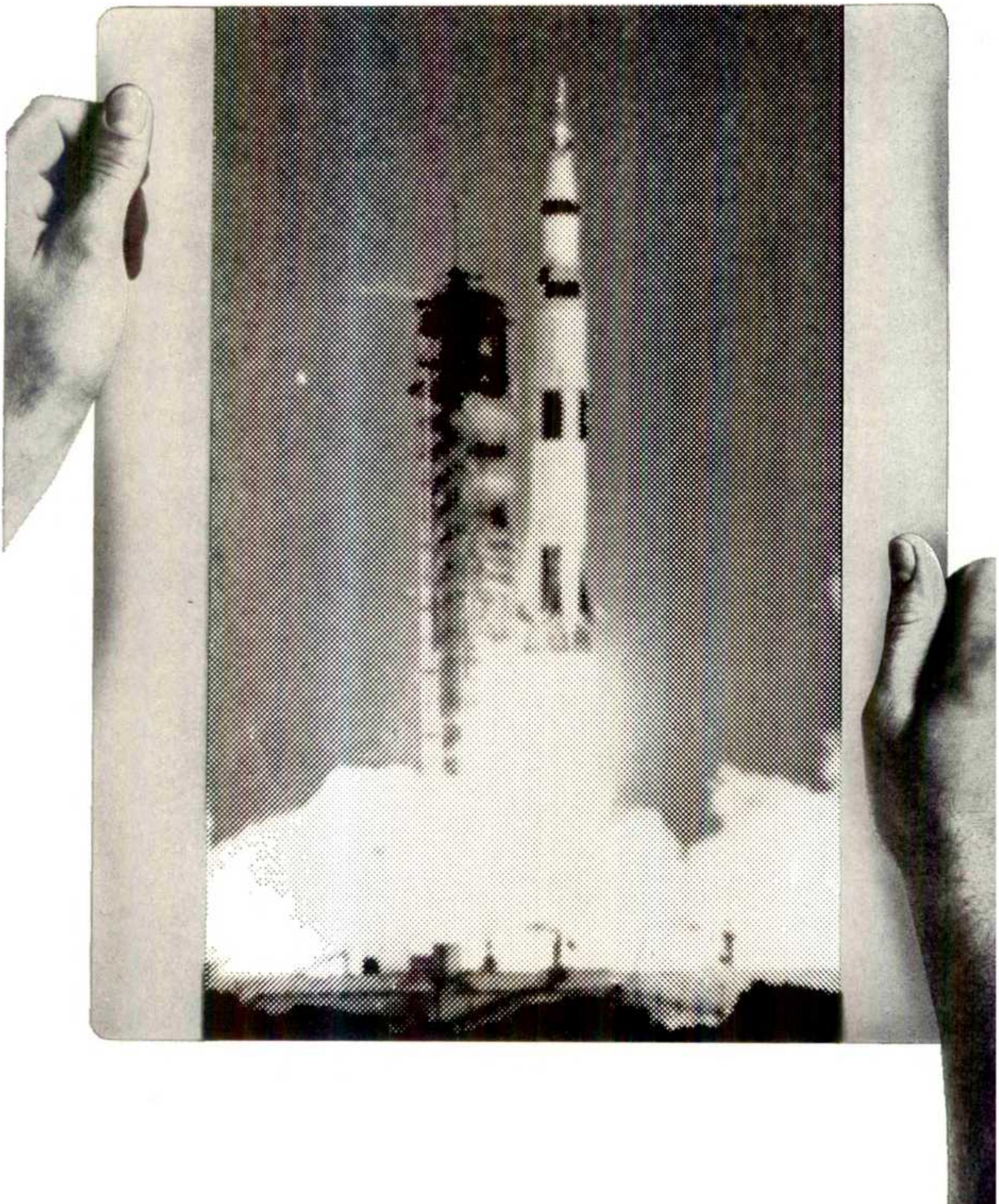
In urography Uromiro combines lower levels of diuresis[2] with active tubular secretion[3] resulting in excellent nephrographic and pyelographic phases.

Uromiro is also well tolerated in a wide range of doses in abdominal and peripheral angiography with minimal and transient side effects[4].

Uromiro–clear new benefits for the radiologist from BDH Pharmaceuticals.

References 1. Bonati et al, (1965) Arzneimittel-Forschung, 15, 222-229. 2. Bellizi, (1966) Radiologica Radioterapia and Fisica Medica, 21, 3. 3. Bollerup et al, (1975) European Journal of Clinical Pharmacology, 9, 63-67 4. Kaude, (1973) Der Radiologe, 13, 271-275

BDH Pharmaceuticals Ltd, Lenten House, Lenten Street, Alton, Hampshire GU34 1JD. Telephone Alton (0420) 88767. Telex 858435. Uromiro and BDH are trade marks.



ILFORD shows up everywhere.

The performance you expect–and get from ILFORD X-ray materials shows up in many other, sometimes unexpected places.

For if there's an image to be recorded, ILFORD will seldom be far away.

Our Microfilm products show up in the computer world recording output and in the fields of finance and industry with image retrieval systems. And again in the security recording of the massive weekly tide of football pool coupons.

We show up again in newspapers and magazines where ILFORD films and papers provide the illustrations which are often converted into print by ILFORD Graphic Arts materials.

Our Photographic products can show up everywhere from banks (Surveillance film for high security areas) to outer space (Nuclear emulsions as used in every U.S. space shot so far).

In Colour Printing too–amateur or professional–Cibachrome shows up wherever standards really count. You may not see the name, but you will see the results–everywhere.

It is this very involvement in so many fields that supports the broad fundamental research and keeps the ILFORD products you use efficient and up-to-date.

One last thing from ILFORD that always 'shows up': the after sales and technical service.

ILFORD X-RAY

ILFORD Limited, Basildon, Essex.

There's more to ILFORD than meets the eye

LUMBAR MYELOGRAPHY

AMIPAQUE MEANS SAFETY

- excellent tolerance, especially with regard to epileptogenic effects.
- adhesive arachnoiditis unlikely to occur.

The excellent tolerance of AMIPAQUE has been confirmed in more than 150 000 examinations covering the various parts of the subarachnoid space.

In lumbar myelography AMIPAQUE – metrizamide – offers better visualization because adequate doses will be well tolerated.

The medullary cone may be included routinely.

NYEGAARD OSLO
P.O. Box 4220 Torshov, Oslo 4, Norway.

Amipaque

Your Scintigraphy Kit

Your kit starts with any of our three simple one-step preparations which combined with our new Sterile Technetium-99m Generator offers a complete package for liver, lung, bone and brain scintigraphy. Later we will be adding more kits to our range.

All our kits are tested extensively in clinical trials which include the use of other technetium-99m generators as well as our own. All are terminally sterilized and every batch is animal tested.

Agent for Bone Scintigraphy

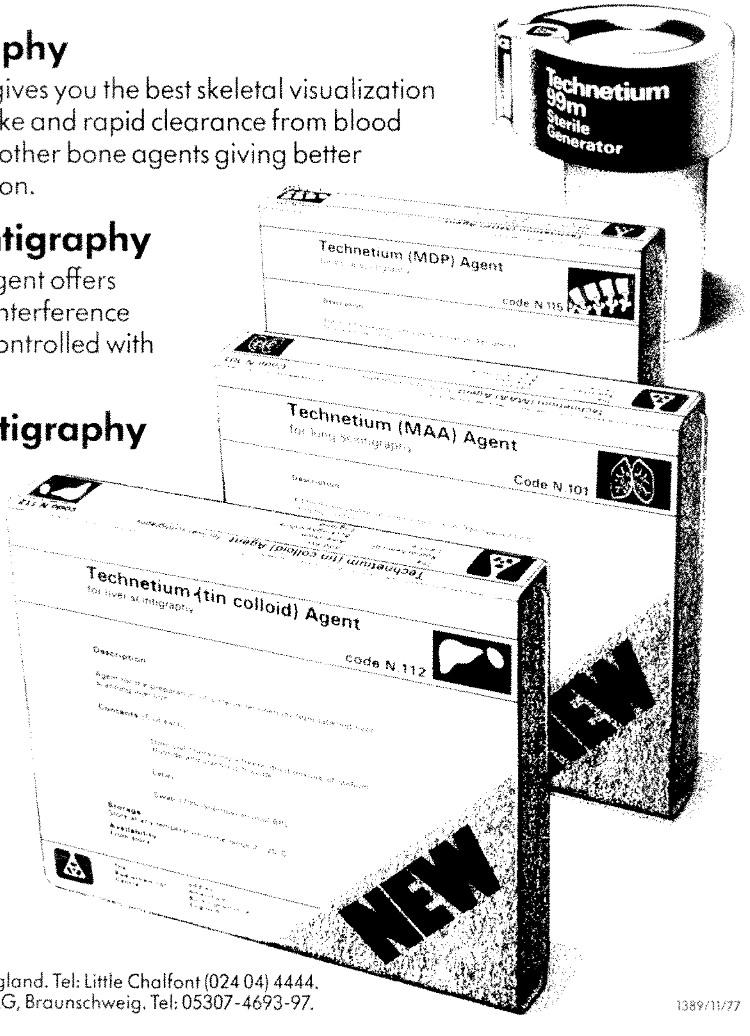
Our Technetium (MDP) Agent gives you the best skeletal visualization available today. The high bone uptake and rapid clearance from blood and soft tissue makes this superior to other bone agents giving better definition and improved discrimination.

New Agent for Lung Scintigraphy

Our new Technetium (MAA) Agent offers detailed lung visualization, with no interference from the liver. Particle size is strictly controlled with the majority in the range of 10–80μ.

New Agent for Liver Scintigraphy

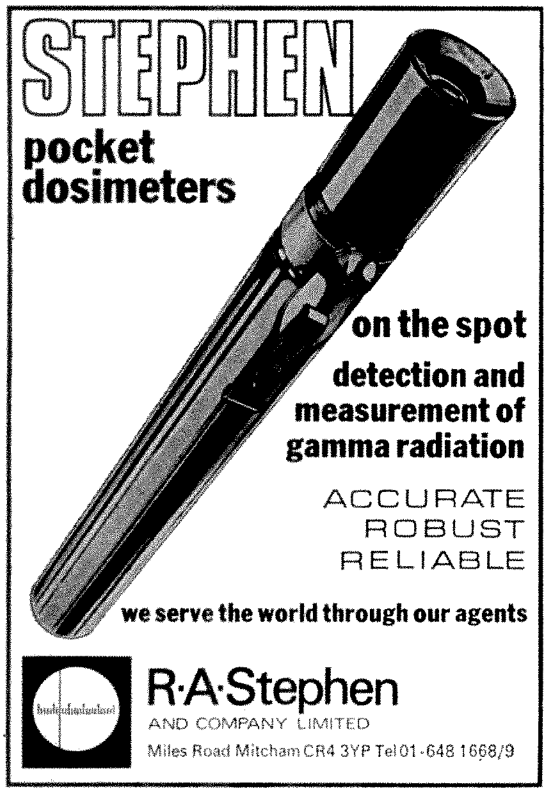
The latest addition to our range is the unique Technetium (tin colloid) Agent. Its preparation is much simpler than sulphur colloid agents and requires no heating stage. It will visualize liver and spleen and unlike agents based on phytate, the colloid is formed in the vial, allowing quality control checks prior to injection.



**The Radiochemical Centre
Amersham**

The Radiochemical Centre Limited, Amersham, England. Tel: Little Chalfont (024 04) 4444.
In W. Germany: Amersham Buchler GmbH & Co, KG, Braunschweig. Tel: 05307-4693-97.

1389/11/77



STEPHEN

pocket dosimeters

on the spot detection and measurement of gamma radiation

ACCURATE
ROBUST
RELIABLE

we serve the world through our agents

R·A·Stephen
AND COMPANY LIMITED
Miles Road Mitcham CR4 3YP Tel 01-648 1668/9

STAFF RADIOLOGIST

Royal Alexandra Hospital for Children

Camperdown (Sydney), N.S.W., 2050.

Australia

Applications are invited from qualified diagnostic radiologists for appointment to the above full-time position in this 500-bed paediatric teaching hospital of the University of Sydney. The Department of Radiology has entered into a major re-equipment programme which is nearing completion. Experience in C.T. Scanning, Ultrasound and Angiography would be an advantage. Other staff members are the Director and one full-time radiologist plus a small number of visiting staff.

Salary in the range $A24,762/$A30,719 per annum with a limited right of private practice within the Health Commission Private Practice Scheme.

Additional information may be obtained from Dr. M. de Silva, Director of Radiology. Applications with curriculum vitae and the names of not less than two referees to J. S. Yu, General Superintendent.

The British Journal of Radiology
Special Report Series

No. 2 *The Use of Computers in Therapeutic Radiology* (1966 International Conference)
70p

No. 3 *The Design of Counting systems for Dynamic Studies and Uptake Measurements* (1968)
£2·40 (Members of BIR £1·70)

No. 4 *Computers in Radiotherapy* (1968 2nd International Conference)
50p

No. 8 *The Design and Installation of Efficient Fume-Cupboards* (1974)
30p

No. 9 *A Survey of Images of a Phantom Produced by Radioisotope Scanners and Cameras* (1976)
£2·50

No. 10 *Treatment Simulators* (*Applications of Modern Technology in Radiotherapy*) (1976)
£1·80

No. 11 *Guidelines for the Preparation of Radiopharmaceuticals in Hospitals* (1975)
£2 (£2·50 overseas by airmail)

No. 12 *The Planning of Radiotherapy Departments*, edited by T. J. Deeley (1976)
Paperback £6·50
Casebound £10·50

No. 13 *Computers in Radiotherapy in Europe* (Proceedings of the European Association of Radiology Workshop, Vienna, July 1976)
£6·80

No. 14 *Considerations about the Use of Computers in Radiodiagnostic Departments*, edited by G. H. du Boulay
£6·75

No. 15 *Clinical and experimental applications of Krypton 81m*, edited by J. P. Lavender
£12·00
ISBN 0 905749 01 4

Available from Publications Office
The British Institute of Radiology
32 Welbeck Street
London W1M 7PG

AGFA-GEVAERT

Contrast, definition, brilliance - in a word, CURIX

Enquiries have proved that most radiologists working with Curix RP1 film prefer the material because of its outstanding qualities.

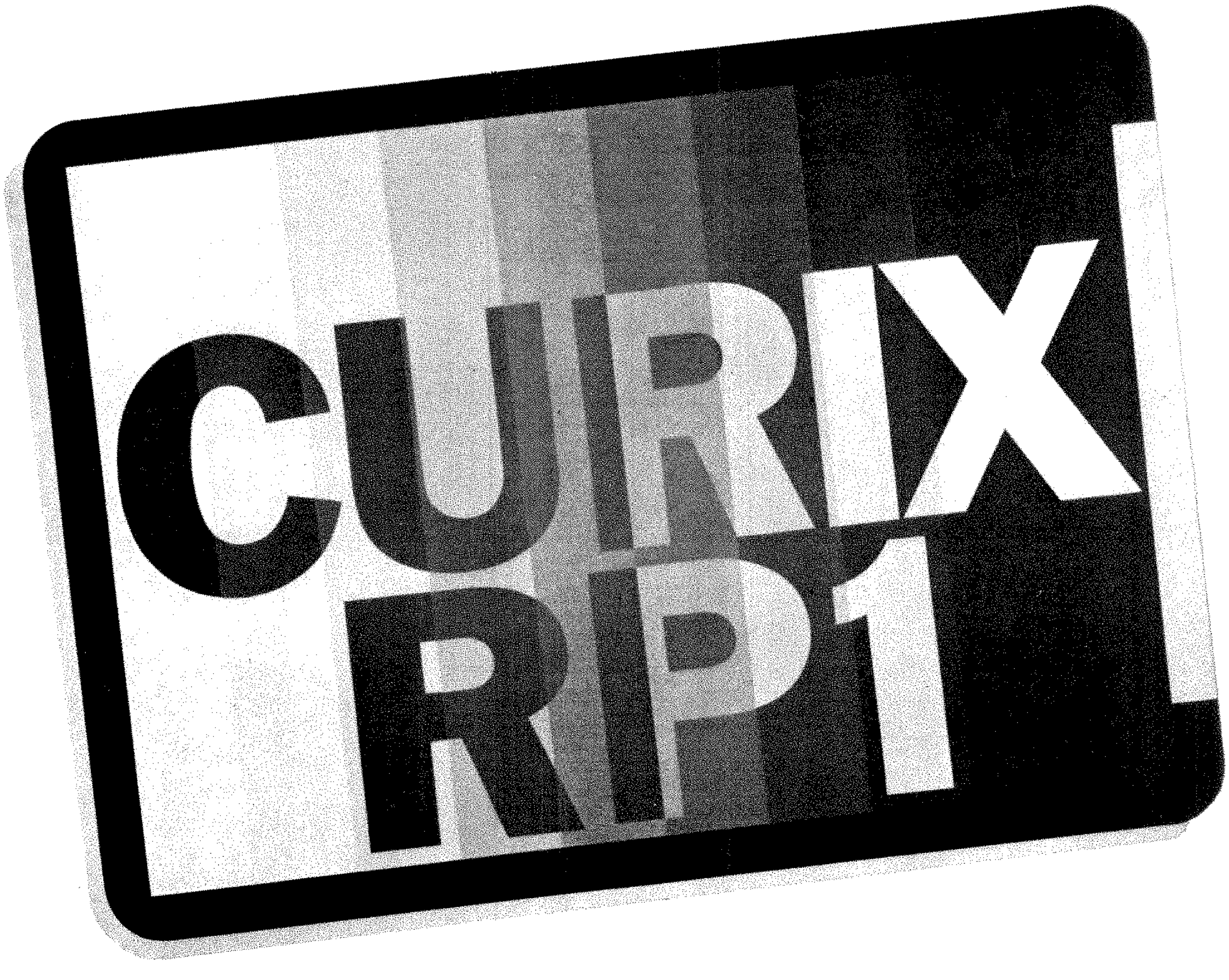
In making their choice, low fog level, contrast, image sharpness and sensitivity were of prime importance. In a word, they required "quality". Curix offers that quality.

The film combines all the desired properties which give the radiologist more detailed information on which to base a safe, sure diagnosis.

It's easy to see why Curix is our biggest selling X-Ray film.

Isn't it time you proved the brilliance of Curix RP1.

Further information from:
Agfa-Gevaert Ltd.,
Medical X-Ray Sales Dept.,
27 Great West Road, Brentford,
Middlesex TW8 9AX.
Tel: 01-560 2131



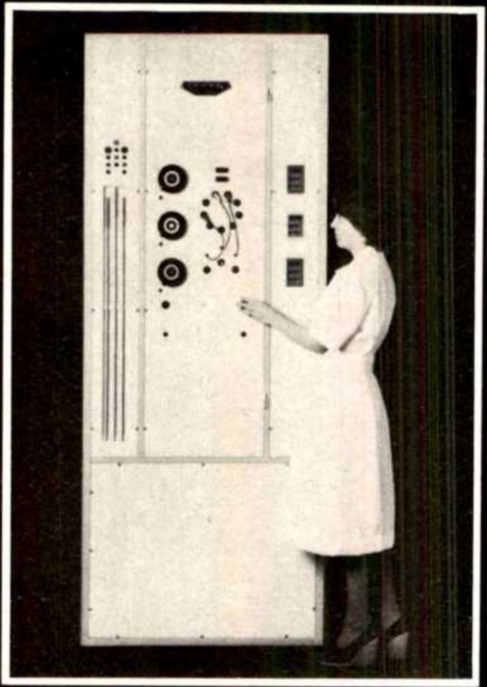
Oldelft

Sure, with a bit of luck and the baby in the correct position you could even distinguish between a boy and a girl....
A bold statement testifying to the amazingly high image definition ensured by Oldelft's Toshiba ultrasound equipment. Toshiba ultrasound proves conclusively that even the finest details of fetal anatomy can be visualized.

This product is handled by:
Oldelft Deltronix bv
Fruitweg 9, 2525 KE Den Haag.
Holland. Tel. (070) 888963.
Telex 32 195.

België/Belgique
2 100 Deurne, Twee Gezusterslaan 34,
Tel. (03 1) 24 93 05.
Deutschland
D 6300 Giessen/Lahn, Postfach 5420
Tel. (064 1) 4 10 49

England
Croydon CRO 1JN, 16 Barclay Road,
Tel. (01) 68 111 71
España
Madrid 16, Uruguay 13,
Tel. (01) 259 1698
France
91403 Orsay, B.P. 86,
Tel. (01) 9075900
Italia
Via della Vasca Navale 84,
Tel. (06) 5584311
Schweiz
8618 Oetwil am See, Zelglistrasse 5,
Tel. (01) 929 13 18.
Sverige
17206 Sundbyberg 6, Postbox 670,
Tel. (08) 98 38 95

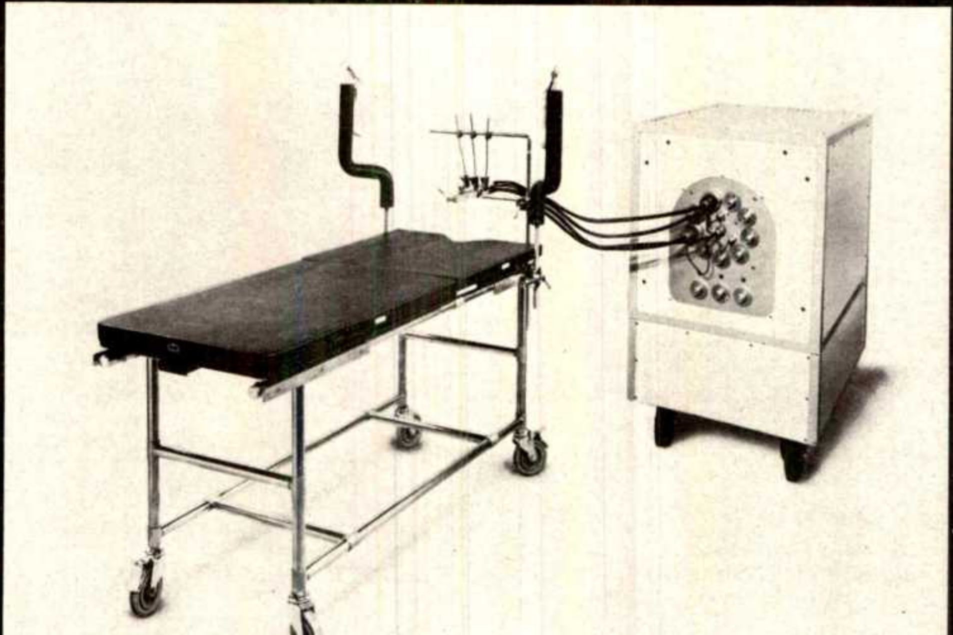


Cathetron
Remote loading Intracavitary unit using Cobalt 60.

The Cathetron has now been in clinical use for over a decade and is used by well over 30 hospitals in nearly 20 different countries.

Use of the Cathetron gives full protection, from radiation hazards, to all staff and reduces treatment time to minutes, thus ensuring that the Catheters stay in their correct location. These short treatment times mean that many patients can be treated as out-patients and therefore need not take up valuable bed space.

The Cathetron is used for surface mould treatments; treatments of the oesophagus and bronchi as well as gynaecological cases.



TEM Instruments Limited

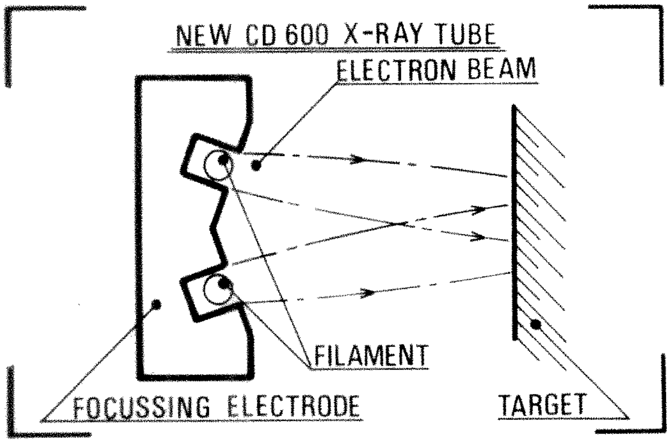
Gatwick Road, Crawley, Sussex, RH10 2RG, England Tel 0293 31244
Telex 87397, Grams TESTMENT CRAWLEY

NEW second generation

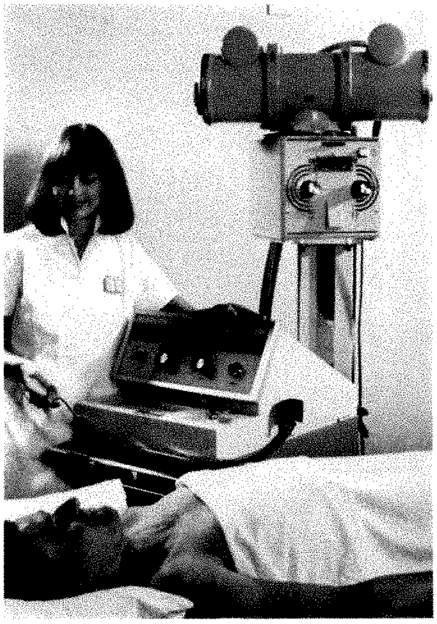
600 m A p

Capacitor Discharge Mobile

- SUPER OUTPUT 600 mAp/125 kVp
- MILLISECOND SWITCHING 2–60 mAs in 15 steps
- IMPROVED MANOEUVRABILITY three forward speeds and two reverse – extra low speed for bedside adjustment
- UNIQUE HIGH POWER CD600 X-RAY TUBE fine focus, high capacity
- LOW COST half cost of cordless systems



NEW CD 600 X-RAY TUBE



The second generation series CD600 capacitor discharge X-ray tubes have been designed on a new principle using a focussing electrode to cut-off the tube current in place of the grid which was previously used.

With this tube, two 0·8 mm focal spots are superimposed on the target slightly shifted from each other. This results in a high power peak intensity distribution over a focal spot effective size 1·2×1·2 mm.

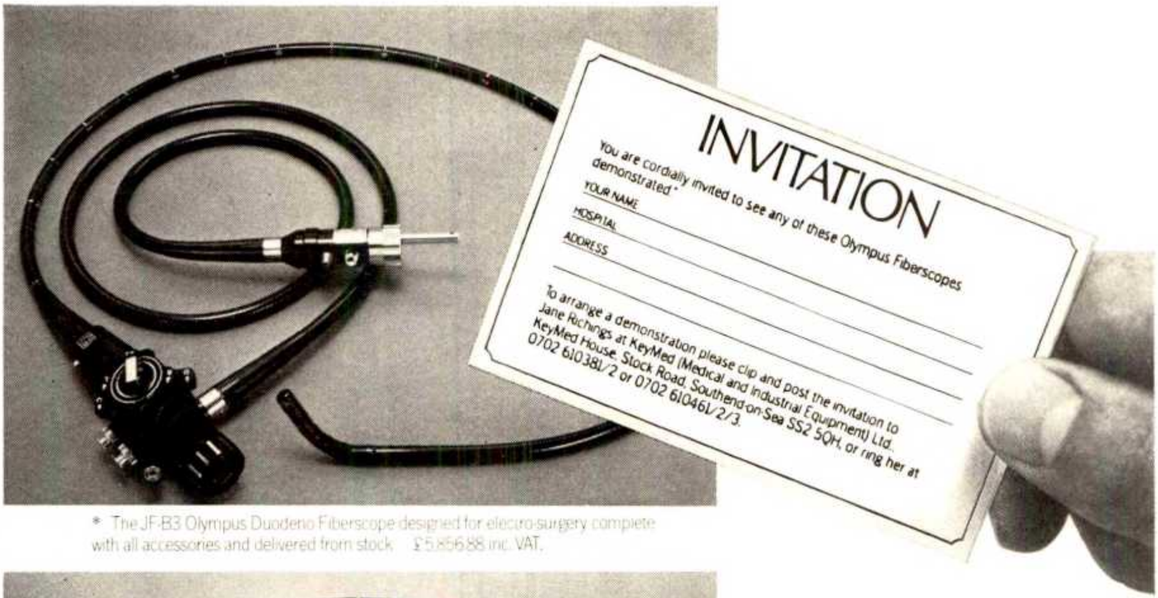
A great improvement is achieved in the Modulation Transfer Function over the conventional tube and therefore excellent detail at high tube mA loadings is achieved.

The use of this double focus combination also reduces individual filament temperature and provides longer tube filament life than conventional tube design.

Before making any decisions, contact us and arrange a demonstration in your own Department.

TODD RESEARCH LTD
ROBJOHNS ROAD
CHELMSFORD CMI 3DP
TEL. (0245) 62233/7 TELEX 99327

*Our 1978–9 catalogue is now available. Contact us and a copy will be mailed by return.



INVITATION

You are cordially invited to see any of these Olympus Fiberscopes demonstrated*

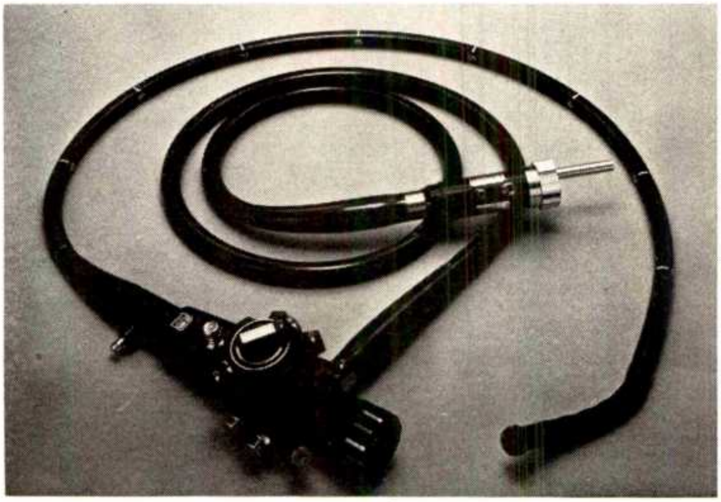
YOUR NAME

HOSPITAL

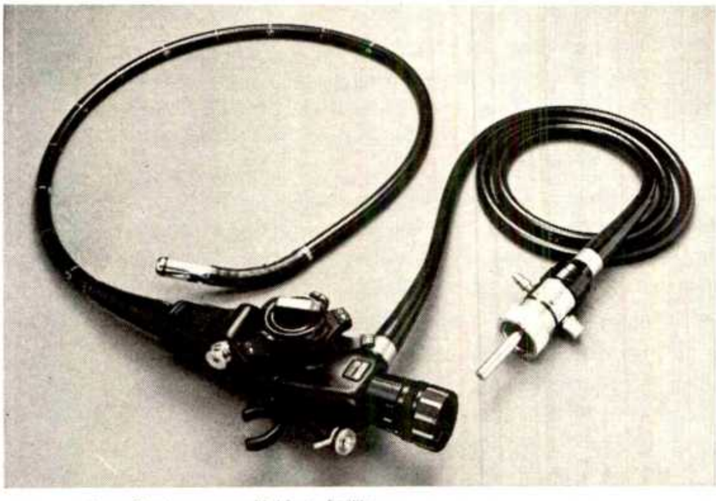
ADDRESS

To arrange a demonstration please clip and post the invitation to Jane Richings at KeyMed (Medical and Industrial Equipment) Ltd., KeyMed House, Stock Road, Southend-on-Sea SS2 5QH, or ring her at 0702 610381/2 or 0702 610461/2/3.

* The JF-B3 Olympus Duodeno Fiberscope designed for electro-surgery complete with all accessories and delivered from stock £5,856.88 inc. VAT.



* The CF-MB3 Olympus Medium Length Colono Fiberscope designed for electro-surgery complete with all accessories and delivered from stock £5,434.60 inc. VAT.



A new Gastro-camera with biopsy facility.

All carry a full one-year guarantee and are backed by a 25-strong team of highly trained technicians, in turn backed by a stock of repair parts worth £160,000, all within an £180,000 fully air-conditioned, de-humidified and air-filtered repair laboratory.

KEYMED

Manufacturers of Specialised Medical Instruments and exclusive distributors in the United Kingdom of

OLYMPUS

Fiberoptic Endoscopes

Illuminators par EXALlence

At Exal we are proud of the reputation we have built up for good design and the high standard of engineering of our products. These qualities are reflected in our range of X-ray Illuminators which is now first choice in hundreds of hospitals throughout the country.
Illustrated above and far left are the new Fullite Illuminators with edge-to-edge viewing providing greater flexibility for vertical and horizontal banking. Near left is the well established Exal unit – robust and attractively finished in grey hard stoved enamel. These units are available as 1, 2, 3 and 4-way models, the multiway units fitted with high-intensity spotlight.
Write for illustrated specifications.

EXAL

EXAL X-RAY ACCESSORIES LTD
MARK ROAD
HEMEL HEMPSTEAD
HERTFORDSHIRE
Tel: Hemel Hempstead (0442) 64401

AXISCAN 5

The new portable real-time ultrasound scanner from Kontron Roche

• Built to a unique design, offering all the facilities you require for obstetric and general abdominal scanning • Truly portable design makes it very easy to use in ante-natal clinics and other departments within hospitals • Simple operation facilitates routine obstetric investigations with the minimum of fuss • Fetal maturity estimations can be established quickly using the integral electronic calipers which automatically reproduce an on-screen digital display. • Results are permanently recorded with the built-in camera. • The excellent grey-scale display shows moving structures up to 25 cm deep. • All our customers are backed by a national 24 hour Kontron Roche service.

KONTRON ROCHE

serving hospitals throughout the world

For further information, please complete the coupon below and post to Dr. Hargreaves, Kontron Instruments Ltd., P.O. Box 188, Watford WD2 4YX or telephone Watford (0923) 47666

Please contact me to arrange a demonstration of/send me further information about/ the Axiscan 5.

NAME. . . . .

POSITION . . . .

ADDRESS. . . . .

. . . .

. . . .

TELEPHONE . . . .

Clinical and Experimental Applications of Krypton 81m

Edited by J.P. Lavender

The British Journal of Radiology, Special Report 15

This work is composed of papers presented at an International Meeting held in June 1977 concerned with a new physiological tool; the use of a very short-lived radioactive gas krypton 81 m.

Krypton 81 m is a noble gas with a 13 second half life available from a portable generator with a half life of 4½ hours. Although known for a number of years it has only been used with any frequency by physiologists and clinicians since 1975.

The first section of the book deals with the production of the parent isotope rubidium 81 and the design of generators. The second section comprises a series of papers concerned with the use of the equilibrium image as both a picture and a measure of regional lung ventilation and perfusion. It also outlines problems of deriving absolute values of lung function. In the third section, papers illustrate the use of krypton 81 m as a clinical tool in the diagnosis of pulmonary embolic disease and other pulmonary diseases and compare such information with that obtained from the more familiar xenon 133. In the last section the use of intra-arterial krypton as a marker of regional myocardial and cerebral blood flow is discussed. This technique, which has been most highly developed in the case of the myocardium, allows detailed images of the myocardial perfusion to be recorded. Perhaps its clearest application is in following rapid changes of regional myocardial perfusion in response to transient ischaemia, stress and drugs.

The discussion following each paper allows an assessment of the value and place of this new technique.

ISBN 0 905749 01 4
ISSN 0306-2120 **Price £12**

Orders to:
Publications,
The British Institute of Radiology,
32 Welbeck Street, London W1M 7PG
(01-935 6237)

or your local bookseller.

APPEAL

A permanent home for British radiology

The Appeal Committee

Sir Jan Lewando, CBE (Chairman)
Dr. Julian Bloom
The Lord Hunt of Fawley, CBE
Mr. Kevin Hughes
Sir Peter Kerley, KCVO, CBE
Professor L. F. Lamerton
Sir Thomas Lodge
Dr. J. F. Loutit, CBE, FRS
Professor W. V. Mayneord, CBE, FRS
Professor J. H. Middlemiss, CMG
The Lord Penney, OM, KBE, FRS
Sir Edward E. Pochin
Sir John Read
Mr. C. F. E. Shakerley
Dr. S. Cochrane Shanks, CBE
Professor Sir David Smithers
Professor R. E. Steiner
Dr. Herman D. Suit
Professor Sir Brian Windeyer
The Lord Zuckerman, OM, KCB, FRS
Professor G. H. du Boulay, Appeal Co-Ordinator

The President of the Institute and Appeal Executive Committee members

Funds are needed to secure a new permanent home for The British Institute of Radiology at 36 Portland Place, London, W1, next door to the Royal College of Radiologists

Donations and ideas to:

Appeal Co-Ordinator, BIR, 32 Welbeck Street, London W1M 7PG (01-935 6237)

1978, *British Journal of Radiology*, *51*, 843–846

VOLUME 51 NUMBER 611 NOVEMBER 1978

The British Journal of Radiology

Radiology now

The ten day rule—principles and practice

Diagnostic radiologists have a two-fold duty to their patients. The first- and prime-duty is to see that an adequate examination is performed so that an accurate diagnosis can be made. The second duty is to ensure that the examination is conducted with the least possible radiation to the patient. Much has been done both in radiological techniques and in the scientific area of design to reduce dose. But new techniques mean that, although the dose per examination may be low, the total dose may be higher as a result of several radiological examinations being required to reach a diagnosis. In all patients there are the general risks of radiation, but in the female there are extra risks to be considered. The area we wish to discuss is the irradiation of the potentially pregnant.

The recommendation that in women of child-bearing capacity non-urgent diagnostic radiography of the abdomen should be confined to the pre-ovulatory phase of the menstrual cycle, *i.e.* the ten days following the first day of the last menstrual period, was made over 20 years ago by the Russells (1955); it was later restated by the International Commission on Radiological Protection (1970). It was contained in the Code of Practice for the Protection of Persons against Ionizing Radiations arising from Medical and Dental Use (1972) and it was endorsed by the report of the Working Party of the Law Commission on Damage to the Unborn Child (1973).

This recommendation in the United Kingdom is known as the "ten day rule". But, of course, it does not truly represent a hard and fast rule and would be better referred to as the "ten day principle". In all women of child bearing age there is a potential risk to an offspring from abdominal X-ray examinations, and this fact should ensure that such radiography is undertaken only after this potential risk has been considered by the doctor requesting the examination.

The application of the ten day principle does not necessarily involve the postponement of all non-urgent abdominal and pelvic radiological examinations of women presenting in the second half of the menstrual cycle.

The majority of patients will be able to give an assurance that they are not pregnant, either by reason of adequate precautions, or by reason of absence of intercourse; only the minority who are unable to give this assurance will need to have the examination deferred till the first part of the next cycle.

The Code of Practice, of course, forbids mass miniature chest radiography for routine use in pregnancy but we do not agree with a suggestion in a personal communication (to C.K.W.) (McCreadie, 1977) that MMR examinations must comply with the "ten day rule".

The Code of Practice forbade the use of mass miniature radiography in pregnancy for three reasons; first the poor diaphragm collimation which would lead to a wider area of irradiation than necessary; second, the higher skin dose; and third, as pregnancy advanced, the poor collimation which would lead to significant irradiation of the fetus and, in particular, to irradiation of the fetal gonads. But with all these factors taken into account, there is still insufficient potential fetal dose in *early* pregnancy to justify enforcing the ten day principle in MMR examinations.

Recently the American College of Radiology, the National Council on Radiation Protection and Measurements in Report No. 54 (1977), the U.S. Department of Health Education and Welfare (Food and Drugs Administration 1976) and scientific workers at some universities in the United States (Brown, 1976; Brown *et al.*, 1976) have been examining the justification for, and the implications of, the Ten Day Principle and they have come to the conclusion that restricting irradiation to the first ten or fourteen days of the menstrual cycle is irrational and might even be disadvantageous (cit.).

NCRP Report No. 54 uses a concept of an elective examination and defines it as one which does not contribute to the diagnosis or treatment of a woman in relation to her immediate illness. There is a further reference in this report suggesting that ICRP agree with this concept but no ICRP report uses this phrase or anything like it. NCRP No. 54 proposes that only these elective examinations should be postponed. Brown *et al.* (1976) use a similar approach that "planned scheduling should only be undertaken for radiological examinations of the abdomen which are not concerned with the current illness". The question must be asked "why should the examination be performed at all if not related to the current illness?". This illustrates the differing outlook between American practice, which would postpone very little, and British practice, which would postpone a considerable number of abdominal examinations if there were a possibility of pregnancy.

There is a concept in NCRP No. 54 that the health of the mother and of the embryo or fetus are synonymous. This cannot always be so. Mother or fetus may require to take precedence. A parallel can be drawn from clinical medicine where an elective operation for peptic ulcer might be desirable, but would not be undertaken during pregnancy.

Brown *et al.* (1976) of the University of California report the quantitative and qualitative risks, as described in the literature, of radiation during preconception and pregnancy. These authors indicate that there may be no advantage in confining radiography of such women to the pre-ovulatory phase since Graham *et al.* (1966) reported data which suggested that the ripening follicle (days 1–10 from the onset of the menses) may be as adversely affected by radiation exposure as the fertilized ovum. These data have not been confirmed but, if true, irradiation at this period could, in fact, be more deleterious biologically than irradiation in the pre-implantation period (days 14–23) when a damaged zygote would probably be lost by abortion. Zygotes which survive are likely to be normal since irradiation at this stage is thought to have all-or-none effects. Both the Russells (1952; 1955) and Rugh (1969) imply that there may be a threshold effect of the order of 10 rad at this stage of pregnancy so that the risks of irradiation by low doses of X rays would be further reduced and may be lower than in the first half of the menstrual cycle. The least dangerous time for conducting a radiological examination in early pregnancy, Brown *et al.* accordingly suggest, might be between days 14 and 28 since the onset of the last period—the exact opposite of what the ten day principle requires. But it must be stressed that the whole of this argument rests on the work of Graham *et al.*, and that no one has confirmed this work.

An examination of Graham's work shows that he and his co-workers used experimental animals (mice and rats) and drew conclusions which other workers strongly suggest cannot be extrapolated to the human being (Baker 1971; Beaumont 1968). There is a different radiation response in different species and different patterns of oogenesis. In the human being the oocyte is probably in a resting phase till 36 hours prior to ovulation (Edwards, 1966)—the onset of the so-called "L H surge". Hereafter radiosensitivity is said (Mandl, 1963) to increase by a factor of ten as the cell passes to metaphase I. The second division is completed in the fallopian tube. Therefore, it would seem logical to suggest that the period of increased sensitivity only begins 36 hours prior to ovulation. With the extra days always allowed in the ten day principle for early ovulation the current practice would appear to be soundly based.

A recent UNSCEAR publication (1977) suggests that, if there is irradiation in the 9 to 40 days following conception, there is some evidence of risk of resulting malformation. If we then realize that days 9–14 after conception are the latter part of the menstrual cycle leading up to the first missed period, the ten day principle avoids irradiating a pregnancy at this time—a time when the mother cannot know she is pregnant as she will not have missed a menstrual period. The risk is, of course, difficult to quantify but extrapolation of the Russells' data suggests a figure of 1 per 2000 per rad. Nevertheless at low doses there may be a threshold phenomenon.

Irradiation during the fetal period (days 65 *et seq*) by the data of Stewart and Kneale (1970) carries a risk of malignancy in childhood estimated at 1:2000 per rad, and Brown *et al.* (1976) comment that postponement of radiological examination to this stage of pregnancy causes approximately the same risk as at any other stage of pregnancy and, by implication, preconception.

From the analysis of these data it could be said that there is no "safe" period during which radiography of the lower abdomen of a woman of reproductive capacity can be carried out. This attitude is accepted by the American College of Radiology. They stress that the possibility of pregnancy should always be considered before abdominal radiography of women of child-bearing age is performed but recommend that planned scheduling should only be undertaken for radiological examinations of the abdomen which are *not* concerned with the patient's current illness.

Can we accept the implications that irradiation pre-conception is as likely to produce the same risk as post-conception? Apart from the unconfirmed work of Graham *et al.* (1966) no supporting evidence is offered by Brown *et al.* (1976). The evidence suggesting the contrary view has been quoted above.

The American documents assume that the examination will always be performed on the same day that the referring doctor sees the patient. In the USA this may well be the normal practice but in the UK the normal practice for examinations with contrast media is to perform them at a booked time so as to spread the work load evenly and waiting lists of 2 or 3 weeks are not uncommon. Therefore, if the examination may have to be delayed for organizational purposes, then in practice it is not difficult to fit in those small number of cases who should conform to the ten day principle. Therefor, in practice, in the UK, the implementation of the ten day principle has not been difficult and has been fairly widespread.

The most recent international pronouncement on the subject is ICRP 26 (1977). This states in paragraph 206, "because of the risk of radiation injury to any embryo or fetus the possibility of pregnancy is one of the factors to be considered in deciding whether to make a radiological examination involving the lower abdomen in a woman of reproductive capacity. Although such an examination is less likely to pose any hazard to a developing embryo if carried out during the "ten day" interval following the onset of menstruation, attention should always be paid to details of radiological technique that would ensure minimization of exposure to any embryo or fetus that may be present whether or not the woman is known to be pregnant".

Does this advice conflict with what we have said above? The recommendation stresses the need to take the possibility of pregnancy into account—but offers no advice, very reasonably, as to what one should do if the patient is pregnant. United Kingdom practice would undoubtedly be to postpone the majority of examinations if the patient were pregnant. The inference, therefore, of paragraph 206 could well be that one should consider very seriously "because of the risk of radiation injury" whether the examination should be carried out or not if the patient were pregnant. Therefore, it would seem to be logical to continue to follow the ten day principle unless there is true clinical urgency rather than clinical convenience.

Again, paragraph 206 goes slightly further and stresses the need to pay attention to radiological technique in examining women of reproductive capacity so that any embryo that might be present receives only a minimal exposure. This recommendation surely is one which should be taken to heart.

We remain unconvinced by the arguments in favour of abandoning the ten day principle and we strongly recommend its continued application, believing it to be an essential part of good radiological and radiographic practice.

We wish to acknowledge with thanks the helpful criticism of our colleagues on the Radiation Protection Committee of the British Institute of Radiology. The views expressed above are, however, entirely those of the authors.

J. H. E. Carmichael,[*]
C. K. Warrick[†]

REFERENCES

Baker, T. G., 1971. The radiosensitivity of mammalian oocytes with particular reference to the human female. *American Journal of Obstetrics and Gynecology*, *110*, 746–761.

Beaumont, H. M., 1968. Proceedings symposium on effects of low radiation doses on the maturation of the developing human ovum and foetus. *British Journal of Radiology*, *41*, 714–722.

Brown, R. F., 1976. Prepared remarks for the October 10, 1976 A.C.R. Press Conference, see also *Wall Street Journal* October 21, 1976.

Brown, R. F., Shaver, J. W., and Lamel, D. A., 1976. *A Concept and Proposal Concerning the Radiation Exposure of Women.* University of California, RHSEP Publication No. 874.

Code of Practice for the Protection of Persons against Ionizing Radiation arising from Medical and Dental Use, 1972. H.M.S.O., London.

Edwards, R. G., 1966. Mammalian eggs in the laboratory. *Scientific American*, *215*, 72–80.

Graham, S., Levin, M. L., Lilienfield, A. M., Schuman, I., Gibson, R., Dowd, J. E., and Hempelmann, L., 1966. "Preconception, and postnatal irradiation as related to leukaemia", in "Irradiation as related to leukaemia". *National Cancer Institute Monograph No. 19*. 347–371.

I.C.R.P., 1970. Recommendations of the International Commission on Radiological Protection. Publication No. 15. para. 174. Pergamon Press, Oxford.

1977. Recommendations of the International Commission on Radiological Protection. Publication No. 26. para. 206. Pergamon Press, Oxford.

Law Commission, 1973. *Injuries to Unborn Children.* Working Paper No. 47. Law Commission, 37, St. John Street, London, WC1N 2BQ.

McCreadie, D. W. A., 1977. Scottish Home and Health Department, Personal Communication.

Mandl, A. M., 1963. The radiosensitivity of oocytes at different stages of maturation. *Proceedings of the Royal Society*, (London) *Series B*. *158*, 119–141.

N.C.R.P., 1977. Report No. 54. *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women.*

Rugh, R., 1969. Proceedings of the Ninth Annual Hanford Biology Symposium—Chairman's Remarks. U.S. Atomic Energy Commission, Division of Technical Information. *AEC Symposium Series 17*, 381–391.

Russell, L. B., and Russsell, W. L., 1952. Irradiation hazards to the embryo and fetus. *Radiology*, *58*, 369.

1955. Hazards to the embryo and fetus from ionizing

---

[*] Broadgreen Hospital, Liverpool L14 3LB

[†] Royal Victoria Infirmary, Newcastle Upon Tyne, NE1 4LP

radiation. Proceedings of the First International Conference on the Peaceful Uses fo Atomic Energy, Geneva, Switzerland. Vol. XI, 175–178.

STEWART, A., and KNEALE, G. W., 1970. Radiation dose effects in relation to obstetric X rays and childhood cancers. *Lancet*, *1*. 1185–1188.

UNSCEAR, 1977. "Sources and Effects of Ionizing Radiation". United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations, New York, 1977. II Effects of Radiation. Section C. 32.

Book reviews

Endometrial Carcinoma and its treatment: the role of irradiation, extent of surgery, and approach to chemotherapy. Edited by L. A. Gray, pp. x+225, 1977 (Charles C. Thomas, Illinois, U.S.A.), $22.50.

This book reports the proceedings of a meeting devoted to the treatment of endometrial carcinoma held in Kentucky in 1975. For the most part the contributors are well known American specialists in this field and the book is largely concerned with analyses of their results after using various combinations of surgery and radiotherapy. In the USA there was a standard practice of using intracavitary radium followed by hysterectomy in all stages of the disease. This book shows clearly that there has been a change in recent times from this routine. Each contributor stresses the important effect which the clinical stage and the histological grade of the tumour have on prognosis and therefore on treatment. Unfortunately no prospective randomized trial is reported and so no firm conclusions are reached. Nevertheless the book contains a great deal of clinical data and the many differences of opinion point to the need for treatment to be tailored to stage and grade.

Contributors make clear that hysterectomy when possible is the best primary treatment and that additional external pelvic irradiation, whether pre- or post-operative, improves survival figures in those cases with deep myometrial invasion or a poorly differentiated tumour. The prevention of vaginal vault recurrence has not been clarified by the results given in this book. For example, if invasion is merely superficial and the tumour well differentiated, particularly when the surgeon removes a generous cuff of vagina, it still remains unclear if intracavitary radiotherapy need be given prophylactically.

The results, even with the less advanced tumours, are not viewed complacently by any contributor and it is therefore surprising that so few have used progestational agents. From the University of Rome, where facilities for intracavitary radiotherapy are not available, encouraging results are reported for a small series of early (and late) tumours treated by hysterectomy with pre- and post-operative progestogens. It is disappointing that the progestogens are not dealt with more fully for advances in treatment probably lie along these lines or in the as yet largely unexplored chemotherapeutic field. Stephen Carter summarizes the present state of cytotoxic chemotherapy and suggests a priority for the agents to be investigated, emphasizing the need for multidisciplinary co-operation.

Parts of the book make very good reading, in particular a review of the development of modern treatment by Saul Gusberg. Another review, from the Memorial Hospital, New York, by Howard Homesley and John Lewis, gives results going back to 1917 and includes figures from the later Brunschwig era of radical surgery. Their present protocols for different stages and grades of tumours are clearly defined and include combinations of pre-operative external pelvic radiotherapy, various forms of hysterectomy and post-operative intracavitary radiotherapy. For the latter they use high intensity cobalt 60 sources and an afterloading technique.

This is a well produced specialist book. It contains nothing new but it will interest clinicians who treat patients with this disease.

THELMA D. BATES.

Grundlagen der medizinischen radiologie (*The basis of medical radiology*). By E. Baudisch, pp. 438, illus., 1978 (VEB Verlag Volk and Gesundheit, Berlin), DM.22.

This book of 438 pages is planned as a synopsis of medical radiology for medical students and junior doctors. It does not claim to be comprehensive. There are useful sections on radiation biology and protection. 218 pages are devoted to diagnostic radiology, 53 to nuclear medicine and therapy and 67 to radiotherapy. The illustrations are positive prints of poor quality so that the lesion cannot always be seen. References are very few and all except two are East German in origin.

The information is very basic and didactic and assumes no knowledge of the subject. It achieves its object of providing a simple primer on medical radiology for the undergraduate student. Since undergraduate medical radiology does not exist as a separate subject in the U.K. and is split into separate disciplines in the postrgaduate field, the book does not fill an obvious need in this country.

G. M. STEINER.

1978, *British Journal of Radiology*, *51*, 847–850

Radiologic manifestations of epidemic haemorrhagic fever with renal syndrome

Yong Whee Bahk, M.D. and Choon Yul Kim, M.D.

Department of Radiology, St. Mary's Hospital, Catholic Medical College, Seoul 100, Korea

(*Received March, 1978*)

ABSTRACT

Epidemic haemorrhagic fever is a viral disease characterized by acute febrile onset followed by profound renal dysfunction. The endemic areas are widespread throughout the Eurasian continent and the Japanese islands. The patient with EHF usually seeks medical care as an emergency for an "acute abdomen". Consequently the X-ray examination becomes an essential part of the clinical study.

We analysed the plain abdomen and chest films of 62 patients with this disease. The radiologic manifestations represented diffuse capillary damage with resultant oedema and haemorrhage, particularly in the retro-peritoneal space. Abnormal findings were seen in 94% of the patients on the plain abdomen, and in 63% on the chest film. The most significant finding was obliteration and blurring of anatomical detail in both intra- and retro-peritoneal cavities and renal enlargement. We believe that simultaneous presence of oedema and effusion in both intra- and retro-peritoneal cavities along with renal enlargement is in practice pathognomic of EHF. Obliteration of the renal outline and cardiomegaly with overt lung oedema was associated with the most severe renal dysfunction.

Epidemic haemorrhagic fever with renal syndrome (EHF) is one of the most important haemorrhagic fevers (Casals *et al.*, 1966). Clinically the disease runs a fairly distinct course of fever, hypotension, oliguria and diuresis, manifesting headache, vomiting, haemorrhage, shock and renal failure (Johnson, 1975). The first cases of EHF were reported from the far eastern side of the Soviet Union under the eponym of Churilov disease during the 1930's (Smordinstev *et al.*, 1963), and until World War II the endemic areas were known only in the Far East. Since then, however, a disease identical to EHF has been reported as nephropathia epidemica in northern Scandinavia (Myhrman, 1951; Fjellström, 1960) and as nephrosonephritis in eastern European countries including the regions west to the Ural Mountains (Casals *et al.*, 1966; Johnson, 1975; Smordinstev *et al.*, 1963) and most recently in Japan (Tamura, 1966). Thus, the disease is now widespread from the Pacific to the Baltic.

It is true that the epidemiology and clinical aspects of EHF are well documented (Casals *et al.*, 1966; Chun, 1965; Counts and Seltser, 1953; Johnson, 1975; Leedham, 1953; Smordinstev *et al.*, 1963; Swift, 1953), and the specific diagnosis can now be made in Korea using an antigen-antibody reaction (Lee and Lee, 1976), but there has been no previous report on the radiology. Moreover, our experience has shown that the radiologic study in the emergency room is very helpful in correctly recognizing this strictly non-surgical "acute abdomen" which, once operated on, ends in catastrophe.

CLINICAL MATERIAL AND METHODS

Sixty-two patients with EHF were admitted to St. Mary's Hospital, Seoul and St. Vincent Hospital, Suwon, Catholic Medical College during the four-year period from January 1970. There were 53 males and nine females, and ages ranged from 18 to 73 years. The diagnosis was made on the basis of typical symptoms, signs and clinical course of the disease (Johnson, 1975). Laboratory tests were used mainly to exclude other diagnostic possibilities (antigen-antibody test was then not available).

Most of the patients were in the oliguric phase and had at least one PA or AP chest film and a plain abdomen. Ten had two to four serial examinations of the chest and abdomen covering the hypotensive, oliguric and diuretic phases, allowing us to make sequential observation of the radiologic changes as the patients recovered from oliguria. In three patients, an intravenous urogram was available.

The X-ray films were read by three radiologists separately. The observers agreed on criteria for diagnosing cardiomegaly, enlargement of the kidney, and widening of the "flank stripe" and interintestinal spaces. Heart size was assessed in terms of the cardiothoracic ratio, the upper normal value of which was set at 50%. A heart with a transverse diameter of more than 15 cm or a difference of more than 1.5 cm in a serial films was considered enlarged. A kidney with a length more than 3.4 times the height of the second lumbar vertebra plus its subjacent disc space was judged to be enlarged (Simon, 1964). A flank stripe measuring more than 3 mm in width at the right lower lateral abdomen (Keeffe *et al.*, 1967) and an interintestinal space wider than 5 mm (Meschan, 1973) were classified as abnormal. In settling disagreement on film reading, we adopted a majority decision or repeated evaluation after full discussion. Finally we correlated the radiologic findings of the chest and abdomen with the blood urea nitrogen (BUN) and serum creatinine levels.

RESULTS

Abnormal findings demonstrated in the chest X ray were lung congestion, oedema, pleural reaction and cardiomegaly (Fig. 1). As shown in Table I, one or more abnormal lung findings were seen in 63% with lung congestion being the most frequent (47%). Pleural reaction was mostly mild with thickening of the minor fissure, blunting of the costophrenic sulcus or tenting of the hemidiaphragm, but in three cases effusion was considerable. Cardiomegaly, mild to moderate in grade, occurred in 21%.

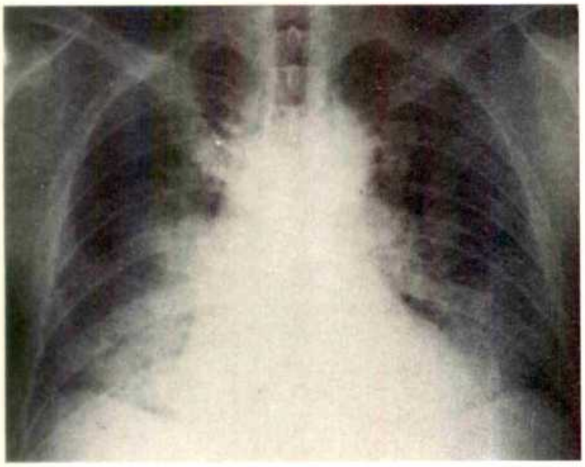


FIG. 1.

Postero-anterior chest revealing diffuse obliteration of alveolar air spaces and increased, blurred vascular markings because of lung oedema and congestion. The heart is moderately enlarged, and the hemidiaphragms are inclined laterally (Hessen sign), representing pleural effusion in the subpulmonary spaces.

The radiologic abnormalities observed in plain views of the abdomen included paralytic ileus with intestinal wall thickening, intra- and/or retro-peritoneal oedema, and renal enlargement (Fig. 2A and B). The frequency with which these radiologic signs occurred is shown in Table I. It is seen that a majority of 94% of patients had one or more abnormal findings in the plain film of the abdomen. In detail, the most frequent finding was widening or blurring of the right flank stripe and interintestinal

TABLE I

RADIOLOGIC FINDINGS OF THE CHEST AND ABDOMEN IN EPIDEMIC HAEMORRHAGIC FEVER

CHEST (abnormal signs in 63% of all patients)	
Lung congestion	47%
Lung oedema	14%
Cardiomegaly	21%
Pleural reaction	32%
ABDOMEN (abnormal signs in 94% of all patients)	
Ascites*	74%
Paralytic ileus†	69%
Obscured renal shadow	53%
Obscured psoas shadow	68%
Enlarged kidney	23%

*Flank-stripe sign, hepatic angle sign.
†With intestinal wall thickening.

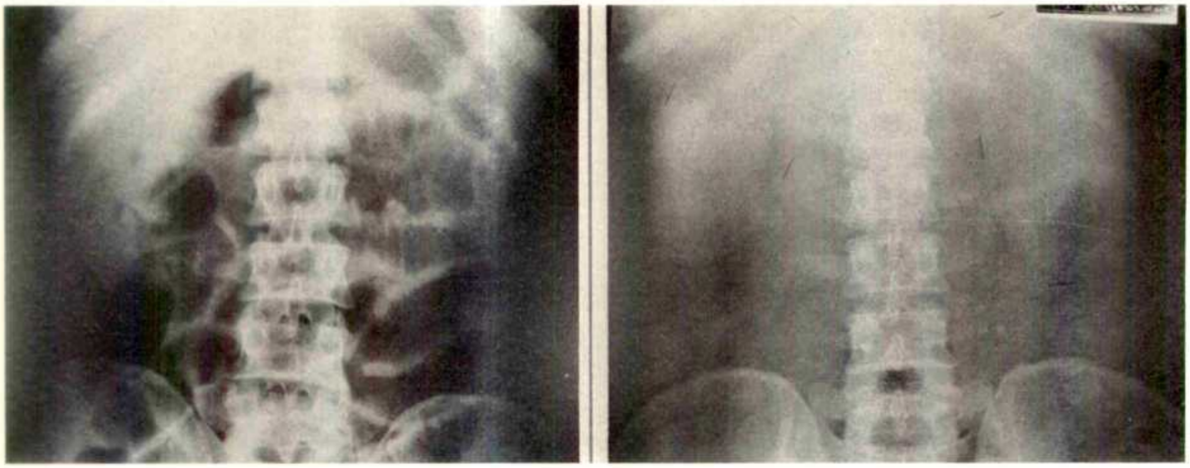


FIG. 2.

(A) Plain abdomen showing diffuse gaseous distension of bowel loops with widening of the interintestinal spaces. The flank stripe is blurred and widened and the hepatic angle obliterated, indicating peritoneal oozing.

(B) Plain abdomen of another patient showing marked enlargement of kidneys, and obliteration of psoas muscle and renal shadows, especially on the right.

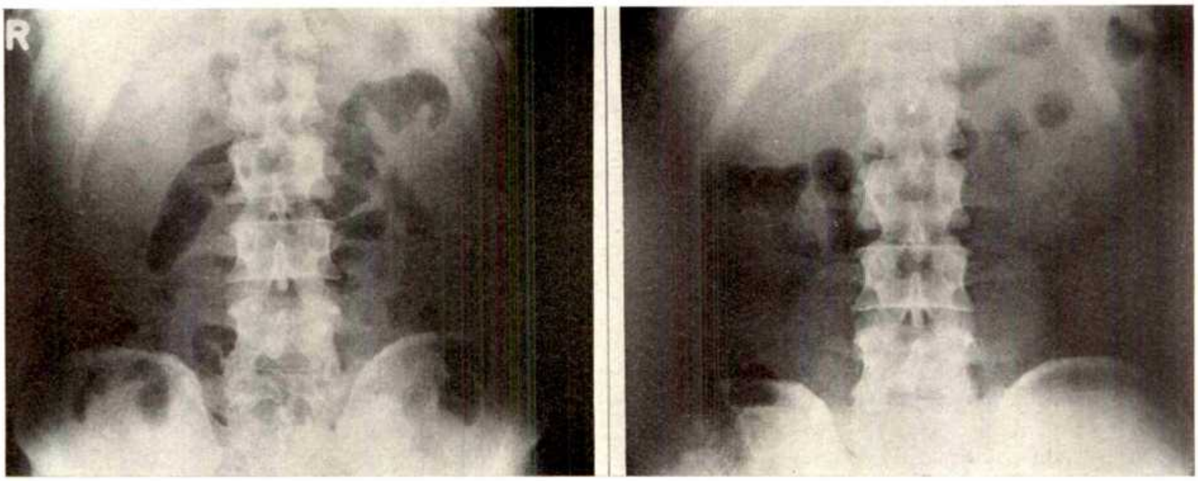


FIG. 3.

Serial study of the abdomen.

(A) Abdomen taken in the hypotensive oliguric phase showing relatively early X-ray changes such as segmental gas distension of the intestine, thickening of the plical markings and intestinal wall. The psoas muscle shadows are blurred but the kidneys not yet enlarged.

(B) Three days later the kidneys became markedly enlarged and the entire abdomen distended.

TABLE II

X RAY FINDINGS OF THE CHEST AND ABDOMEN RELATED TO RENAL FUNCTION TESTS

	BUN (mean) (mg/dl)	Creatinine (mean) (mg/dl)
CHEST		
Cardiomegaly	116	9.9
Lung congestion	98	9.0
Lung oedema	95	9.2
Pleural reaction	96	9.1
ABDOMEN		
Obscured renal shadow	103	8.7
Obscured psoas shadow	91	7.1
Ascites	92	7.1
Paralytic ileus	89	6.5
Enlarged kidney	66	4.6

spaces. The next most common finding was retro-peritoneal oedema as represented by the obliteration of either the psoas muscle shadow and/or renal outline. Paralytic ileus with thickening of the small bowel wall and plical markings was seen in 69%, and renal enlargement in at least 23%. The renal outline could not be seen due to retro-peritoneal oedema or oozing in 53%, and in all probability the kidney was enlarged in these cases. We made serial observations in ten patients, from which it emerged that early radiologic signs were intestinal paralysis, intestinal oedema and ascites. Such peritoneal changes were followed by retro-peritoneal oedema and cardiopulmonary lesions as the oliguric phase deepened (Fig. 3A and B). Clearing of lung congestion and oedema took place rapidly as the patient recovered from the oliguric state. Of ten cases, five showed rapid improvement of the radiologic abnormalities over one or two days, two slow regression and three little or no change while the clinical symptoms improved.

Intravenous urography was available in three patients who were in the oliguric phase. In two of these, the excretion of the injected contrast medium from the kidneys was grossly impaired, and in the remainder there was no discernible excretion of the contrast medium up to one hour.

Correlation of radiologic findings with BUN and serum creatinine levels revealed that obliteration of the renal outline and cardiomegaly with overt lung oedema were associated with the most pronounced increase in BUN and creatinine (Table II). On the other hand, renal function was only modestly impaired when renal enlargement was not attended by retro-peritoneal oozing. The chest lesions occurred in those with severe renal dysfunction.

DISCUSSION

In essence, the radiologic findings of the disease are the graphic representation of the pathologic changes of organs and tissues at the macroscopic level. It is therefore pertinent to review these.

According to Hullinghorst and Steer (1953) and Kessler (1953), EHF is characterized by generalized congestion, oedema and haemorrhage due to capillary damage which is manifest by dilatation, engorgement, increased permeability, rupture and diapedesis of the red blood cells. The oedema involving loose areolar tissues of the retro-peritoneum is most striking. Oedema and haemorrhage are extensive, involving not only the retro-peritoneal space but also the omentum, pleural cavity, mediastinal space and pericardium. The kidney, lung, intestine and central nervous system are more or less regularly invaded. The areolar tissues become distended and swollen with clear straw-coloured fluid which gives rise to a gelatinous appearance. The liver and spleen are usually not grossly changed. In particular, the kidney shows classic lesions. The medulla is always markedly congested and haemorrhagic and the cortex contrastingly pale making a sharp demarcation between the two zones (Hullunghorst and Steer, 1953).

Our study disclosed radiologic signs of diffuse capillary damage in 94% of the plain abdomen and 63% of the chest films. Obliteration of the anatomical details both in the intra- and retro-peritoneal cavities was most impressive. Another important X-ray finding was renal enlargement which occurred in 23%, although this figure did not include 53% of patients whose renal outlines were obscured by retro-peritoneal oedema and haemorrhage. It is therefore apparent that the true incidence of renal enlargement should be the sum of both figures because in all probability the kidney in the latter group is enlarged. Hullinghorst and Steer (1953) have already pointed out that the most conspicuous and important pathologic changes of EHF are the oedema involving the retro-peritoneal areolar tissues and renal enlargement, and this is clearly borne out by our radiologic observation. It is our belief that obliteration of anatomical detail in both intra- and retro-peritoneal cavities along with renal enlargement and intestinal thickening is in practice pathognomonic of EHF.

It is worthy emphasizing that the patient with EHF usually seeks medical care as an emergency for "acute abdomen", and the X-ray of the abdomen often reveals findings very similar to those in panperitonitis. However, correct recognition of the characteristic features of EHF helps to differentiate this non-surgical condition from a surgical emergency. By peritoneal dialysis and supportive treatment we can now save more than 95% of the patients.

Finally it is interesting to note that obliteration of the renal outline and cardiomegaly with overt lung oedema were associated with the most profound renal dysfunction and with a grave prognosis.

ACKNOWLEDGMENT

The authors wish to thank Mrs Hee Sup Choi for secretarial assistance.

REFERENCES

CASALS, J., HOOGSTRAAL, H., JOHNSON, K. M., SHELOKOV, A., WIEBENGA, H. H., and WORK, T. H., 1966. A current appraisal of hemorrhagic fevers in the U.S.S.R. *American Journal of Tropical Medicine and Hygiene*, *15*, 751–764.

CHUN, C., 1965. Epidemic hemorrhagic fever in Korea. *Korean Medical Journal*, *10*, 547–553.

COUNTS, E. F., and SELTSER, R., 1953. The early diagnosis of epidemic haemorrhagic fever – experiences in the forward echelons of the medical service. *Annals of Internal Medicine*, *38*, 67–72.

FJELLSTRÖM, K. E., 1960. Nephropathia epidemica in Uppland. *Acta Medica Scandinavica*, *167*, 111–120.

HULLINGHORST, R. L. and STEER, A., 1953. Pathology of of epidemic haemorrhagic fever. *Annals of Internal Medicine*, *38*, 77–101.

JOHNSON, M. J., 1975. Epidemic hemorrhagic fever. In *Textbook of Medicine*, Ed. Beeson. P. B. and McDermott, W. 14th edition. pp.244–245 Saunders, Philadelphia.

KEEFFE, E. J., GAGLIARDI, R. A., and PFISTER, R. C., 1967. The roentgenographic evaluation of ascites. *American Journal of Roentgenology*, *101*, 388–396.

KESSLER, W. H., 1953. Gross anatomic features found in 27 autopsies of epidemic haemorrhagic fever. *Annals of Internal Medicine*, *38*, 73–76.

LEE, W. H., and LEE, P. W., 1976. Demonstration of causative antigen and antibiotics of Korean epidemic haemorrhagic fever. *Korean Journal of Internal Medicine*, *19*, 371–383.

LEEDHAM, C. L., 1953. Epidemic haemorrhagic fever. A summarization. *Annals of Internal Medicine*, *38*, 106–112.

MESCHAN, I., 1973. *Analysis of Roentgen Signs*, vol. 3, p.1232. (Saunders, Philadelphia).

MYHRMAN, G., 1951. Nephropathia epidemica. A new infectious disease in northern Scandinavia. *Acta Medica Scandinavica*, *140*, 52–56.

SIMON, A. L., 1964. Normal renal size. An absolute criterion. *American Journal of Roentgenology*, *92*, 270–272.

SMORDINSTEV, A. A. KAZBINSTEV, L. I., and CHUDAKOV, V. G., 1963 (Isreal program for scientific translation, Jerusalem, 1964). Virus haemorrhagic fevers. *Cimiz gosudarstvennoe izdatel'stvo meditsinskoi literatury*. Leningrad, U.S.S.R.

SWIFT, W. E., jr. 1953. Clinical aspects of the renal phase of epidemic haemorrhagic fever. *Annals of Internal Medicine*, *38*, 102–105.

TAMURA, M., 1966. Epidemic haemorrhagic fever. *Japanese Journal of Infectious Disease*, *40*, 286–294.

1978, *British Journal of Radiology*, *51*, 851–854

Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage

By Z. F. Boulis, F.R.C.S.(Eng.), F.R.C.S.(Ed.), F.R.C.S.(Glasg.), R. Dick, M.R.A.C.R., F.R.C.R.
The Royal Free Hospital, Pond Street, London NW3 2QG
and N. R. Barnes, C.S.R.T.(Canada)
Enfield District Hospital

(*Received March, 1978*)

ABSTRAST

One thousand and thirty-two consecutive children with head injuries have been studied. All were outpatients, and 1000 had X-rays requested and performed. Of those X-rayed, only 21 (2.1%) had fractures, whilst 129 cases (12.9%) required admission for observation. No patient developed complications from their injuries. The presence or absence of a fracture neither correlated with the clinical situation nor affected the management. The fact that two thirds of all new casualty attendances at UK hospitals have an X-ray examination (*British Medical Journal*, 1977) is an unjustified wastage. Much of this wastage is related to skull X-rays in trauma, especially in children. In only a minority of patients does the presence of a fracture result in any modification of treatment. Some suggestions as to indications for skull X-rays in trauma have been made to help select patients for radiography and to avert wastage.

Head injuries are now more common that ever. It is estimated that a quarter of a million such injuries are treated by hospitals in the UK annually (Jennett, 1969). A large proportion of these are children. Nearly all have skull X-rays. It will be shown that many of these X-rays are unnecessary. This is the first outpatient study on head injuries in children done in England, previous studies being based on admitted cases only (Craft *et al.*, 1972; Devadiga, 1975; Field, 1976; Ghooi *et al.*, 1976).

MATERIAL AND METHODS

During a 17-month period 1000 children below the age of 12, had skull X-rays either for isolated head injury or as part of multiple injuries. A skull unit was used in all cases. Three views were done routinely (lateral horizontal ray, OF 20° down, Townes). Repeat examinations and/or additional views were sometimes necessary. All films were reported by either a consultant or a senior registrar, and reviewed together with the clinical notes. Patients with nasal bone fractures were not included in the fracture group, but other facial bone fractures and fractures of the vault were. Falls from bicycles were considered as accidental injuries rather than road traffic accidents (RTA).

RESULTS

The incidence of symptoms, fractures and soft tissue injuries is shown in Table I. Table II shows the age and sex distribution, males outnumbering females by 9:5. The types of injuries were analysed (Table III). Accidental injuries made up the largest group (93.2%), these being mainly the results of falls at home, school or playground. RTA's constituted only 5.5.% of cases. The non-accidental injuries (battered baby syndrome) and assaults (fights

TABLE I

ANALYSIS OF CASES

Number of cases	Admitted	With fractures	With soft tissue injury to head	With symptoms
1000	129 (12.9%)	21 (2.1%)	722 (72.2%)	350 (35%)

TABLE II

AGE AND SEX DISTRIBUTION

Age (years)	Males	Females	Total	Fracture group
0–1	33	35	68	6
1–4	231	138	369	6
4–8	200	127	327	3
8–12	180	56	236	6
	644	356	1000	21

TABLE III

TYPE OF INJURY

Type of injury	Number of cases	Fracture group
Accidental	932 (93.2%)	19
RTA	55 (5.5%)	2
Non-accidental	10 (1.0%)	—
Assault	3 (0.3%)	—

with other children) constituted a small group totalling 1.3%.

Those with clinical symptoms totalled 350 (35%)—(Table I). Many of these had multiple complaints which were very varied. Unconsciousness was overestimated and headache underestimated. Many head injuries occurred in the absence of parents who, being doubtful about unconsciousness, used vague terms such as "dazed", "became pale" or "momentarily lost consciousness." These were all interpreted as unconsciousness by the casualty officer. "Headache" is a subjective complaint and the very young cannot or do not complain of it. Thus only those with a definite complaint had it recorded. Vomiting, on the other hand, is an objective symptom, and the figures are realistic whatever the child's age. It was the commonest symptom (170 patients) (Table IV). This is not surprising since it is a frequent happening in many conditions affecting children, including uncomplicated head injury. Drowsiness is another objective symptom, and the figures are realistic. Only one predominant symptom was entered per patient in the fracture group, vomiting and drowsiness being the commonest.

None of the patients had significant or permanent neurological signs. Some had transient pupillary signs, perhaps due to local eye trauma. Normal children up to the age of two years may also have Babinski's sign.

TABLE IV

Symptoms

Type of symptom	Total number of occurrence	Predominant symptom in fracture group
Vomiting	170	6
Drowsiness	105	6
Headache	97	2
Unconsciousness	72	5
Other symptoms	27	2

Signs of soft tissue injury to the head were carefully elicited (Table V). Eleven of the 21 patients with fractures had no soft tissue injury. On the other hand, in children soft tissue injury is common following minor trauma, and is frequently seen without underlying fracture. Of 21 patients (2.1%) with fractures demonstrated on X-ray, 18 involved the skull vault and three the facial bones. In a large American head injury outpatient series (all ages), fractures were discovered in 6.2% (Bell and Loop, 1971), and in another series of children 8.6% (Roberts and Shopfner, 1972). One hundred and twenty-nine patients (12.9%) were admitted, including the 21 with fractures. One hundred and twenty (93%) were kept for less than 48 hours, as this is the critical period for a complication to develop. Only nine patients (7%) were kept for more than 48 hours (Table VI). Six non-accidental injuries had social problems to be sorted out, and three had multiple injuries.

Discussion

Head injury is one of the indications for skull X-rays, but several authors (Bell and Loop, 1971; Roberts and Shopfner, 1972) have emphasized the fact that such X-rays cannot be justified in the routine care of the patient with head trauma since skull X-ray is one of the examples where "the yield no longer justifies the expenditure" (Evans, 1977).

The presence or absence of a fracture seldom affects treatment but it is a valuable sign for the following reasons (Jennett, 1969):

TABLE VI

Length of stay in hospital

Duration of stay	Number of cases
24 hours	108
48 hours	12
48 hours +	9
	129

TABLE V

Type of soft tissue injury

Total with soft tissue injury	Total with fracture	Total lacerations	With fracture	Total haematomas	With fracture	Total contusions	With fracture
722	10	405	2	175	3	142	5

1. It may indicate the likelihood of complications, such as an extracerebral haematoma if the fracture line crosses the middle meningeal artery or the lateral sinus.

2. If the fracture line travels to the posterior fossa, a haematoma at this unusual site may be suspected in the event of deterioration.

3. A fracture involving the frontal, ethmoidal or sphenoidal sinuses carries the risk of a dural tear and possible meningitis.

4. Intracranial air, though rare (Roberts and Shopfner, 1972), indicates a dural fistula.

5. Petrous temporal fractures carry a substantial risk of delayed facial palsy. Recognition of this fracture allows timely treatment with steroids to prevent facial palsy.

6. A depressed fracture under a laceration is a compound fracture calling for formal debridment and prophylactic antibiotics.

All of the above serious fractures are rare, and do not justify routine skull X-rays in trauma. The current indications for radiographic skull examinations in trauma are, at best, inexact and generally ill-defined (Bell and Loop, 1971). In our opinion, *skull X rays are suggested only in the following categories:*

1. *Coma:* a fracture or sutural diastasis may be the only evidence of head injury in a comatose patient.

2. *Unconsciousness or drowsiness:* these are the most important symptoms in connection with intracranial complications. The number of patients with unconsciousness or drowsiness was 114. It is highly significant that the overall incidence of these symptoms in 1000 patients was 11%, whereas in the fracture group it was 52%.

3. *Laceration of the scalp:* it might seem absurd to advocate X-rays for this sign alone as the overall incidence of laceration is 40%, yet in the fracture group it was only 9.5% (Table V). However, if a fracture with an overlying laceration is missed, osteomyelitis and possible intracranial infection may be the outcome. We agree with those who advocate skull radiography whenever there is a scalp wound (Miller and Jennett, 1968; Paediatric Symposium, 1965).

4. *Medico-legal cases:* as many as 44% of all X-ray requests from the casualty department are made exclusively for medico-legal reasons (Evans, 1977). We recommend that only the RTA's and assaults be X-rayed, as these may become medico-legal. Certainly if no medical considerations exist to justify skull X-rays in head injury, then it is a "sine qua non" that no legal considerations exist (Roberts and Shopfner, 1972).

5. *Location of suspected foreign bodies.*

6. *Rhinorrhoea and/or otorrhoea.*

7. *Positive neurological findings.*

Those patients not in the above categories should not be X rayed but must be given the usual head injury instructions and re-examined the following day. Those who develop significant symptoms or signs should then be X-rayed and may have to be admitted. This was done routinely for our patients under review.

If we apply the above indications to our series, those patients requiring X-rays would number 640 only, comprised as follows: unconsciousness and drowsiness 177; laceration of the scalp 405; suspected medico-legal cases 58. Those who need not have been X-rayed would be 360 patients (34.8%).

CONCLUSION

This study of 1000 children having skull X-rays for trauma has demonstrated that no correlation exists between symptoms, physical findings, and the likelihood of a fracture on skull X-ray. It was also apparent that there is a significant wastage of skull X-rays. At an average cost of £6 per skull series, *i.e.* £6000 for 1000 examinations, the cost of finding each fracture was £300. If the above indications for skull X-rays had been followed, and 360 not X-rayed, a saving of over £2000 would have been made. Although the extent of injury to the intracranial contents is of major importance, the mere presence or absence of a fracture will seldom determine treatment (Evans, 1977). Hence the above guidelines have been worked out in the hope that "the yield will justify the expenditure in X-ray departments" in children with head injuries.

The present increase in the incidence of head injuries coupled with the adoption of skull X-rays in the routine management of any head "trauma", will increase the cost to X-ray departments and to the National Health Service in addition to the small but definite radiation hazard involved.

ACKNOWLEDGMENT

The help of Dr. K. Lavers, Dr. E. El-Shaama and Mr. G. L. Mouzas of Enfield District Hospital is gratefully acknowledged by Z. F. Boulis and N. R. Barnes.

REFERENCES

BELL, R. S., and LOOP, J. W., 1971. The utility and futility of radiographic skull examinations for trauma. *New England Journal of Medicine*, *284*, 236–239.

British Medical Journal, 1977. Clinical audit in diagnostic radiology. Leading article. *2*, 479.

CRAFT, A. W., SHAW, D. A., and CARTLIDGE, N. E. F., 1972. Head injuries in children. *British Medical Journal*, *4*, 200–203.

DEVADIGA, K. V., 1975. Head injury in children. *Indian Journal of Paediatrics*, *42*, 291–297.

EVANS, K. T., 1977. The radiologist's dilemma. *British Journal of Radiology*, *50*, 299–300.

FIELD, J. H., 1976. *Epidemiology of head injuries in England and Wales*, Department of Health and Social Security Publication, 9.

GHOOI, A. M., KHANNA, T., and GUPTA, M. M., 1976. An analysis of 500 cases of head injury in children. *Indian Journal of Paediatricts*, *43*, 191–197.

JENNETT, W. B., 1969. Head injuries. In *Recent advances in surgery*, 7th edn, 590–621. (J. & A. Churchill Ltd., London).

MILLER, J. D., and JENNETT, W. B., 1968. Complications of depressed skull fracture. *Lancet*, *2*, 991–995.

PAEDIATRIC SYMPOSIUM, 1965. Pitfalls in neurology. *Pediatric Clinics of North America*, *12*, 189–195.

ROBERTS, F., and SHOPFNER, C. E., 1972. Plain skull roentgenograms in children with head trauma. *American Journal of Roentgenology*, *114*, 230–240.

Book reviews

Ultrasound: Its applications in Medicine and Biology. Parts 1 and 2. Edited by F. J. Fry, pp. 745, illus., 1978 (The Netherlands, Elsevier Scientific Publishing Co.), $72.75/Dfl 178.

This two-part book is Volume 3 of a series entitled "Methods and phenomena: their applications in science and technology". If book titles are chosen to indicate the scope of the material within them then here one might anticipate detailed descriptions of the applications of ultrasound, a topic of considerable interest to the radiologist. However, what is presented is a collection of descriptions of the phenomena of ultrasound, subject matter more suitable for readers with a physics or engineering background.

Part 1 contains eight chapters, the first being a very detailed description of the physical principles of ultrasound, abounding in mathematical equations and decidedly short of diagrams. The editor claims that it provides an analytical framework for investigators; it fulfils this assertion admirably. Similarly the second chapter, devoted to cavitation, provides an excellent analysis and a thorough review of experimental studies. Chapter III deals with Doppler principles and techniques. Here we meet the first clinical applications. The last 30 pages of the 120-page chapter deal with arterial occlusive disease, investigated non-invasively and successfully. Chapter IV reverts to the physics theme with a detailed account of transducers while Chapter V deals with the problems of measuring the field. The interaction of ultrasound and real materials occupies the final three chapters with contributions on absorption and dispersion, scattering and impedance profiling.

Part 2 contains six chapters, the first two dealing with bioeffects, chapter IX the non-thermal mechanisms and chapter X the use of physiotherapy. Chapter XI is of most interest to the radiologist as it deals with pulse echo visualization, starting with a relatively (for this book) simple treatment of the physics and concluding with some good examples of actual scans. Chapter XII is unusual in that it deals in depth with a limited topic, a research approach to visualization of breast tumours by ultrasonic methods. Chapter XIII gives an account of the ultrasound microscope and the acoustic characterisation of tissue. The final chapter, XIV, is concerned with the production, effects and use of intense focussed ultrasound. The book concludes with two appendices, summaries of cavitation effects and thermal effects of ultrasound.

Each chapter in this book is written by a leading expert in the field and consequently each chapter is of a very high standard and has an extensive list of references. There are overlaps between chapters but as the work will be used for reference this is of little importance. It is unfortunate that the title is so misleading, because though this collection does not deal with the applications of ultrasound it provides an excellent survey of the phenomenon of ultrasound. Not really suitable for the radiologist because of its lack of clinical material, it is however a valuable book for every physicist and engineer.

M. HALLIWELL.

Gallium-67 Imaging. Edited by P. B. Hoffer, C. Bekerman and R. E. Henkin, pp. xiv+174, 1978 (John Wiley and Sons, New York, Chichester), £14·00.

This book is the most recent addition to the publisher's series of monographs on diagnostic and therapeutic radiology, and its purpose is to describe in a concise volume the present state of the art of the clinical applications of ^{67}Ga.

The book is divided into three sections, each with illustrated chapters contributed by specialist authors. The first section is on fundamentals, comprising a short chapter on mechanisms of localization of the radioisotope, a chapter in which imaging technique is comprehensively discussed with particular reference to selection of channel width(s) and collimator, choice of instrumentation, patient preparation, and radiation dosimetry, and a third chapter in which normal patterns of uptake are considered. Subsequent sections deal with the clinical role of gallium 67 in the diagnosis of inflammatory and neoplastic disease. Emphasis is given to the relative value of radiography, ultrasound and ^{67}Ga imaging in the diagnosis of intra-abdominal abscess, and the section on neoplastic disease includes a chapter on childhood malignancies. At the end of each chapter is a comprenehsive list of references.

At the price of £14·00 the book is perhaps more suitable for purchase by departments than by individuals. It is a valuable reference work recommended for the bookshelf of radioisotope imaging units using ^{67}Ga.

E. J. WOOD.

1978, *British Journal of Radiology*, *51*, 855–857

Visualization of the cystic artery after injection of Pancreozymin

By Z. Chudáček, M.D.

Department of Radiology of the University Hospital in Plzeň, Czechoslovakia

(*Received April, 1978*)

ABSTRACT

In 84 patients selective angiography of the common hepatic artery before and after injection of Pancreozymin was performed. The results prove that:

1. Pancreozymin produces visualization of the cystic artery and its branches and of the gall-bladder wall in the majority of these normal gall-bladders that are not visualized during angiography without Pancreozymin.
2. Pancreozymin improves visualization of many normal and pathological gall-bladders seen only faintly on angiography without Pancreozymin.
3. In a patient with an angiographically normal liver the non-visualization of the branches of the cystic artery or of the gall-bladder wall after injection of Pancreozymin is a reliable sign of organic gall-bladder disease, or of a collapsed gall-bladder seen sometimes in patients with bile duct or pancreatic tumour.

Angiography of the coeliac, mesenteric and hepatic arteries can be useful in detecting gall-bladder diseases. The cystic artery and its branches can be seen in the arterial phase of angiography, the gall-bladder wall can be visualized when the wall stains with contrast medium. In the jaundiced patients the angiographic visualization of the gall-bladder can be very useful.

The purpose of this report is to summarize our experience with Pancreozymin (Boots Company) in selective angiography of the common hepatic artery. Pancreozymin was used in order to improve visualization of the cystic artery and its branches.

METHODS

Selective arteriography of hepatic artery was performed first without Pancreozymin, then five minutes after an injection of, on average, 100 units of Pancreozymin, in the hepatic artery. Angiographic findings were compared with those obtained during surgery or autopsy or with the results of cholangiographic examination.

RESULTS

We used Pancreozymin in 84 selective arteriographies of the hepatic artery; 39 of those were performed in jaundic patients.

In 29 patients either visualization of the cystic artery was absent or only a stump of the cystic artery was seen. In 17 of them the cystic artery and its branches were seen after an injection of Pancreozymin. Among them were ten patients with a normal gall-bladder, four with a gall-bladder inflammation and three with malignant tumours of the gall-bladder, the pancreas or the bile duct (Figs. 1–4).

In 12 patients Pancreozymin did not improve visualization of the cystic artery. These included five cases of advanced gall-bladder inflammation, two cases of malignant tumours of the pancreas or bile duct with a small gall-bladder, one case of liver cirrhosis and four cases of multiple liver metastases with normal gall-bladders.

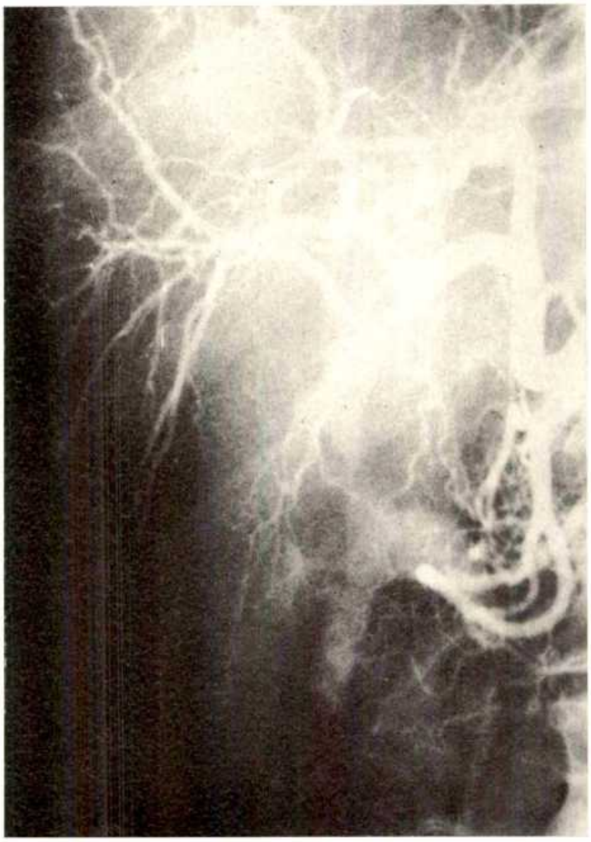


FIG. 1.

Before injection of Pancreozymin: non-visualization of the branches of the cystic artery.

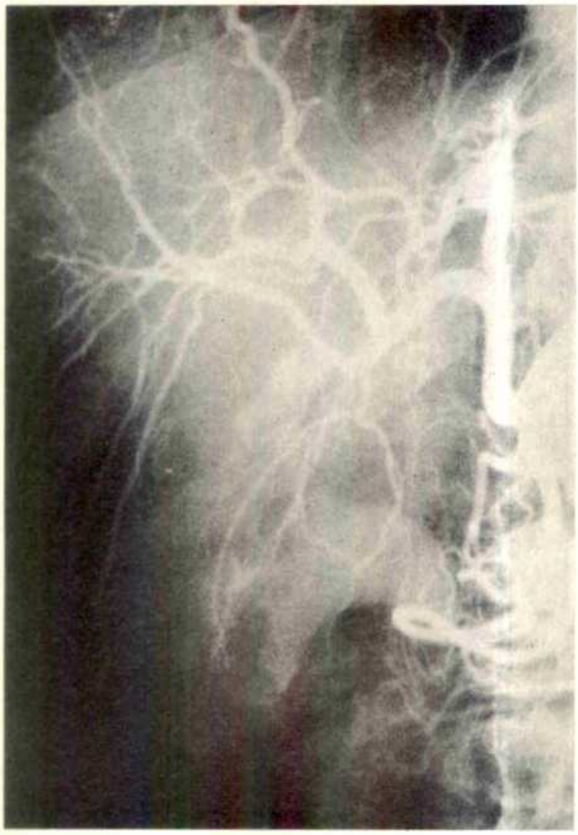


FIG. 2.

After injection of Pancreozymin good visualization of the branches of the cystic artery.

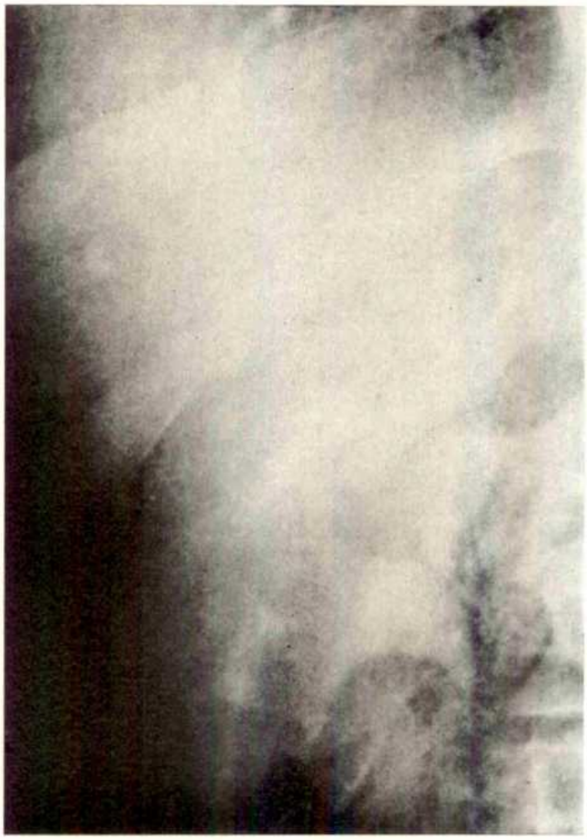


FIG. 3.

In the same patient before injection of Pancreozymin non-visualization of the gall-bladder wall.

In 55 patients the cystic artery, its branches and the gall-bladder wall were already seen during the first examination. Pancreozymin improved visualization in 35 patients, in that the branches of the cystic artery were seen around the whole gall-bladder and opacification of the gall-bladder wall with contrast medium was more intense.

In all patients the contraction of the gall-bladder after an injection of Pancreozymin was investigated. Pancreozymin evoked contraction in 14 patients with a normal gall-bladder. In 34 cases it was not possible to evaluate gall-bladder contraction (among them were 29 patients in whom angiography without Pancreozymin did not evoke visualization of the cystic artery). In 36 patients Pancreozymin did not cause any contraction. These included 18 cases of gall-bladder inflammation either with dilated or shrunken gall-bladder, seven dilated gall-bladders due to tumours occluding the distal bile duct, one case of liver metastases, one case of gall-bladder tumour and nine normal gall-bladders.

DISCUSSION AND CONCLUSION

The following problems occur in the angiographic diagnosis of gall-bladder diseases:

1. Visualization of the cystic artery is absent in many normal gall-bladders.
2. Branches of the cystic and hepatic arteries cannot always be distinguished.
3. Opacification of the gall-bladder wall is often faint.

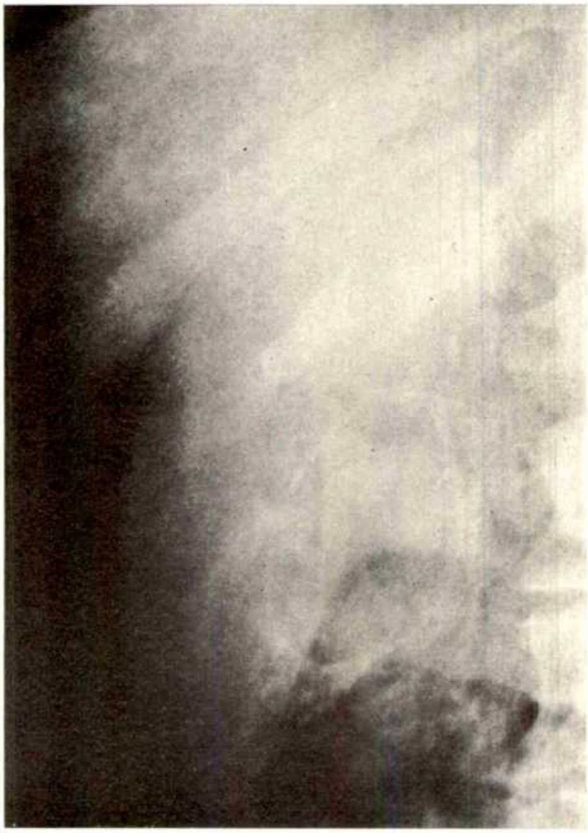


FIG. 4.

After injection of Pancreozymin the gall-bladder wall is well seen.

Udén (1971) published the first report concerning use of Pancreozymin in the visualization of the cystic artery. He concluded that Pancreozymin enlarges not only the hepatic and pancreatic arteries but also the cystic artery. Pancreozymin causes contraction of the gall-bladder because it contains also Cholecystokinin. Udén's conclusions were based on 20 patients.

In 1974–77 we used Pancreozymin in 84 patients to improve the visualization of the gall-bladder. Our results proved:

(a) Pancreozymin produces visualization of the cystic artery and its branches in most of the cases in which they are not seen during angiography without Pancreozymin.

(b) Pancreozymin improves visualization of many normal and pathological gall-bladders seen only faintly during angiography without Pancreozymin.

(c) Pancreozymin causes contraction of the majority of normal gall-bladders.

(d) In a patient with an angiographically normal liver the non-visualization of the branches of the cystic artery or of the gall-bladder wall after injection of Pancreozymin is a reliable indirect sign of organic gall-bladder disease, or of a collapsed gall-bladder sometimes seen in patients with tumours of the bile duct or pancreas.

REFERENCE

UDÉN, R., 1971. Cholecystokinin—pancreozymin in celiac and superior mesenteric angiography. *Acta Radiologica Diagnosis*, *12*, 363–374.

Book review

Hip Arthrography. By Paul Grech pp. xii, +106, illus., 1977 (Chapman & Hall, London and Andover) £8·50.

Arthrography is one of those procedures that one does or not according to ones enthusiasm or that of orthopaedic colleagues. To do an occasional arthrogram is probably as valueless and dangerous as an occasional mammogram. But if the stimulus is there, how does one begin? The answer is now easy, thanks to Dr. Grech.

Here at last is a handbook of fluent—almost conversational—style which sets out in straightforward terms when, why and how to perform arthrography of the hip. Taking us through the anatomy and technique, he then describes the difficulties and complications likely to be encountered, illustrated at one point by a very candid confession of an error of judgement by himself. The moral he points need not deter the beginner for, as with other invasive investigations, if one follows the precepts laid down the complications are minimal.

This slim handbook of about 100 pages is clearly illustrated and invaluable for anyone commencing arthrography of the hip (or indeed any joint) and would be read with advantage by any orthopaedic surgeon or radiologist and should certainly be read by all radiological trainees.

J. T. PATTON.

1978, *British Journal of Radiology*, *51*, 858–861

Hepatobiliary imaging: a comparison of ^{99}Tc^{m}-dihydrothioctic acid and ^{99}Tc^{m}-pyridoxylidene glutamate in the non-jaundiced patient

By R. E. Jenner, F.R.C.S., E. R. Howard, M.S., F.R.C.S., M. B. Clarke, B.Sc. and J. J. Barrett, M.Sc., M.R.C.P.

Departments of Surgery, Medical Physics and Nuclear Medicine, King's College Hospital, London SE5 8RX

(*Received September, 1977 and in revised form March, 1978*)

ABSTRACT

A comparison of two hepatobiliary imaging agents, ^{99}Tc^{m}-dihydrothioctic acid (^{99}Tc^{m}-DHT) and ^{99}Tc^{m}-pyridoxylidene glutamate (^{99}Tc^{m}-PG) has been carried out in 44 non-jaundiced patients. Thirty-one patients were admitted for investigation of upper abdominal pain and 13 patients were volunteers who were undergoing treatment for unrelated conditions. Satisfactory liver images were obtained with both agents in patients without liver disease, but they were inferior to those seen after ^{99}Tc^{m}-sulphur colloid. ^{99}Tc^{m}-PG produced clearer images of the gall-bladder and bile ducts than ^{99}Tc^{m}-DHT.

Non-visualization of the gall-bladder was interpreted as gall-bladder disease; in patients with inflammatory gall-bladder disease no gall-bladder image was seen (nine ^{99}Tc^{m}-DHT, nine ^{99}Tc^{m}-PG). The gall-bladder was also not demonstrated in two of the volunteers' group (one ^{99}Tc^{m}-DHT, one ^{99}Tc^{m}-PG), nor was a gall-bladder seen in five patients whose abdominal pain was not due to acute cholecystitis. Despite this, there was agreement between the results of imaging and oral cholecystography in 21 out of 22 subjects. ^{99}Tc^{m}-PG is non-toxic, cheap and rapidly excreted by the liver into the bile. A ^{99}Tc^{m}-PG scan would be useful when rapid diagnosis is required in suspected acute cholecystitis when conventional contrast radiology is unlikely to be of value.

Recently interest has been rekindled in the simple and atraumatic technique of hepatobiliary scanning which depends on the uptake of radioactive isotope from the blood by liver cells and its subsequent excretion into bile. The early hepatobiliary compounds were labelled with ^{131}I which gives a poor image with a gamma camera, but reports of newer hepatobiliary imaging agents labelled with ^{99}Tc^{m} suggest that they may be of clinical value (Eikman *et al.*, 1975; Ronai *et al.*, 1975; Matolo *et al.*, 1976, 1977). In a previous paper, we have shown that successive images of the liver, gall-bladder and intestine were consistently obtained in normal piglets after injection of ^{99}Tc^{m}-dihydrothioctic acid (^{99}Tc^{m}-DHT) and ^{99}Tc^{m}-pyridoxylidene glutamate (^{99}Tc^{m}-PG) (Jenner *et al.*, 1976). The present study was undertaken to investigate the usefulness of hepatobiliary scanning in non-jaundiced patients with upper abdominal pain. ^{99}Tc^{m}-DHT and ^{99}Tc^{m}-PG were chosen for comparison because they are excreted into bile at different rates and because they are both easily labelled with ^{99}Tc^{m}.

MATERIALS AND METHODS

Ethical Committee approval was obtained for this study in which 44 hepatobiliary scans (21 ^{99}Tc^{m}-DHT and 23 ^{99}Tc^{m}-PG) were carried out. Liver function tests (LFT) were estimated in all patients on an SMA 12/60 autoanalyser, and were considered abnormal when at least one of the following was elevated—total bilirubin (TB), alkaline phosphatase (AP), aspartate transaminase (AST). Two groups of patients were scanned. Group I: "normal" volunteers, 13 patients who had no clinical evidence of hepatobiliary disease (six ^{99}Tc^{m}-DHT, seven ^{99}Tc^{m}-PG scans). Group II: 31 patients admitted either with abdominal pain or for investigation of suspected hepatobiliary disease whose total bilirubin was less than 50 μmol/l (15 ^{99}Tc^{m}-DHT and 16 ^{99}Tc^{m}-PG).

All Group I patients were over 40 years old (average age 61 years) and were scanned unstarved using a Nuclear Enterprises Mark IV gamma camera placed anteriorly over the abdomen. Scanning was started five minutes after injection and continued for one hour after injection of ^{99}Tc^{m}-PG, and for three hours after injection of ^{99}Tc^{m}-DHT. On average ten serial images were recorded on polaroid film containing 400k counts and were assessed independently by one of us (J.J.B.). Patients in Group II (average age 54 years) were scanned within a week of admission and were scanned until either the gall-bladder or a definite intestinal image was evident. Clinical circumstances required four patients to be starved, and the last seven patients in this group were scanned with an Elscint gamma camera.

^{99}Tc^{m}-DHT was prepared from a kit and analysed by ascending thin layer chromatography according to the manufacturer's instructions (3M Company). ^{99}Tc^{m}-PG was also prepared in a kit as recommended by Ronai (1975): pyridoxal hydrochloride 270 mg (Merck), and monosodium glutamate monohydrate 250 mg (British Drug Houses) were dissolved in 5 ml of water for injection and the pH adjusted to 8.5 to 9.0 using 1M NaOH. The mixture was made up to 10 ml with more water and then filtered through a millipore filter into five vials. Each vial was flushed with nitrogen gas passed through a millipore filter and stored at 4°C for up to three weeks. Labelling was achieved by adding 4 mCi $^{99}TcO_4$ (made up to 2 ml with normal saline) and autoclaved for one hour at 120°C. ^{99}Tc^{m}-PG was analysed as described by Baker *et al.* (1975). The percentage of free pertechnetate averaged 1.7% and 1.0% for ^{99}Tc^{m}-DHT and ^{99}Tc^{m}-PG respectively. A dose of 4 mCi was administered to both groups.

RESULTS

No untoward reactions were observed in any patient after administration of either hepatobiliary imaging agent. Table I records the results in both groups of patients.

Group I, $^{99}Tc^{m}$-DHT

Although some background activity was present in all the scans a good quality liver image was seen in five out of six patients. The common bile duct was not demonstrated in any scan, but the gall-bladder and intestine were visualized in four and five scans respectively. Biliary excretion of ^{99}Tc^{m}-DHT was slow, the clearest gall-bladder images occurred on average more than two hours after injection. One patient had a poor quality liver image and no gall-bladder image, but further investigations revealed unsuspected liver and gall-bladder disease (raised AST, AP) with a non-functioning gall-bladder containing a gall-stone. The other negative gall-bladder image was probably false even though the patient had eaten a fatty meal two hours before the scan. Laparotomy one week later (for polypectomy of the transverse colon) revealed a normal looking gall-bladder. An oral cholecystogram was not performed.

TABLE I

HEPATOBILIARY IMAGING WITH ^{99}Tc^{m}-DHT AND ^{99}Tc^{m}-PG IN PATIENTS WITH ABDOMINAL PAIN AND VOLUNTEERS WITH UNRELATED CONDITIONS

	No.	Liver	Gall-bladder	Common bile duct
Group I (normal)				
^{99}Tc^{m}-DHT	6	6	4*	0
^{99}Tc^{m}-PG	7	7	6	6
Group II (abdominal pain)				
(a) *Gall-bladder disease*				
^{99}Tc^{m}-DHT	8	8	0	0
^{99}Tc^{m}-PG	10†	10	0	8
(b) *Non-gall-bladder disease (normal LFT)*				
^{99}Tc^{m}-DHT	3	3	3	0
^{99}Tc^{m}-PG	1	1	1	1
(c) *Non-gall-bladder disease (abnormal LFT)*				
^{99}Tc^{m}-DHT	4	4	0	0
^{99}Tc^{m}-PG	5	5	4	4

*A non-functioning gall-bladder and solitary gall-stone subsequently discovered in one patient.

†Includes one cholecystectomized patient.

$^{99}Tc^{m}$-PG

Satisfactory liver images were obtained in all seven patients, but owing to the rapid transit of isotope through the liver the image was always brief and sometimes uneven. In contrast to the ^{99}Tc^{m}-DHT scans biliary imaging was rapid and clear, the common bile duct and gall-bladder were seen in six scans (Fig. 1) and the gall-bladder appeared on average 25 minutes after injection. Similarly, the intestine was always demonstrated and was seen

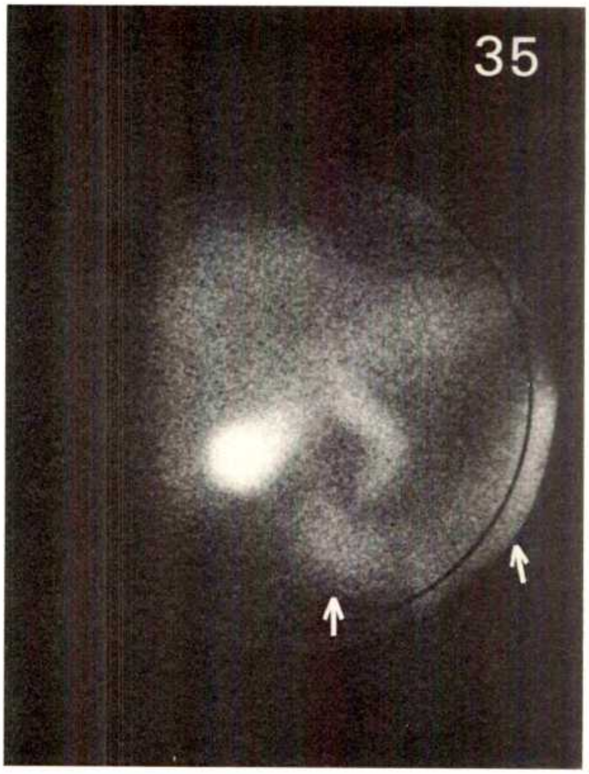


FIG. 1.

^{99}Tc^{m}-PG scan 35 minutes after injection in a normal patient. The liver, gall-bladder, common bile duct and intestine (arrowed) are clearly demonstrated.

earlier than with ^{99}Tc^{m}-DHT scanning. One man aged 66 years with normal LFT had a false-negative gall-bladder image in spite of good liver and intestinal images. The gall-bladder appeared normal at laparotomy one week later (during aorto-femoral bypass) and a postoperative oral cholecystogram was normal.

Group II, ^{99}Tc^{m}-DHT (15 patients)

Liver images of satisfactory quality were obtained in 11 patients, but in four out of six patients with abnormal LFT a poor quality liver image was seen. The early phase of the scan was helpful in one patient whose diagnosis on admission was empyema of the gall-bladder and in whom liver pathology was not clinically suspected. The scan demonstrated a large filling defect in the right lobe of the liver, and laparotomy revealed liver metastases. The ^{99}Tc^{m}-DHT scan correctly diagnosed gall-bladder disease in eight patients on the basis of a negative gall-bladder image. However, the gall-bladder was not seen in four patients (three of whom had abnormal LFT) whose disease was not due to cholecystitis.

^{99}Tc^{m}-PG (16 patients)

The liver was clearly demonstrated in 15 scans, the one poor liver image being obtained in a patient whose jaundice had just resolved: an unevenness of the liver image was noted in four patients. In common with Group I patients, rapid and clear biliary images were again observed and both liver and gall-bladder images were less adversely affected by abnormal LFT. Whereas the common bile duct was not seen in any ^{99}Tc^{m}-DHT scan, it was well demonstrated in three-quarters of the ^{99}Tc^{m}-PG scans. Nine patients had acute gall-bladder disease and in all of them the scan did not show a gall-bladder image (Fig. 2), the same finding as another patient who had previously undergone cholecystectomy. One false-negative gall-bladder image was seen in a patient in whom laparotomy and biopsy revealed retroperitoneal lymphoma and a normal extrahepatic biliary tract. In another patient with acute pancreatitis the scan suggested a normal gall-bladder before oral cholecystography. A gall-bladder image was seen in two patients with parenchymal liver disease.

In summary, the gall-bladder was not visualized in any of the 17 patients who were shown by histology, oral cholecystography, or intravenous cholangiography to have gall-bladder disease. The gall-bladder, however, was not seen in five cases where the primary pathology did not involve the gall-bladder. Four of these patients were scanned with ^{99}Tc^{m}-DHT and four patients had abnormal liver function. By comparison, oral cholecystography showed 15 out of 22 patients to have gall-bladder disease, but in three of the seven patients who did not have gall-bladder disease the gall-bladder was also opacified poorly or not at all. These 3 patients had abnormal LFTs and gave false-negative gall-bladder images with ^{99}Tc^{m}-DHT. ^{99}Tc^{m}-sulphur colloid scans were requested in four patients and the quality of the liver image was always better than either the ^{99}Tc^{m}-DHT or ^{99}Tc^{m}-PG liver image.

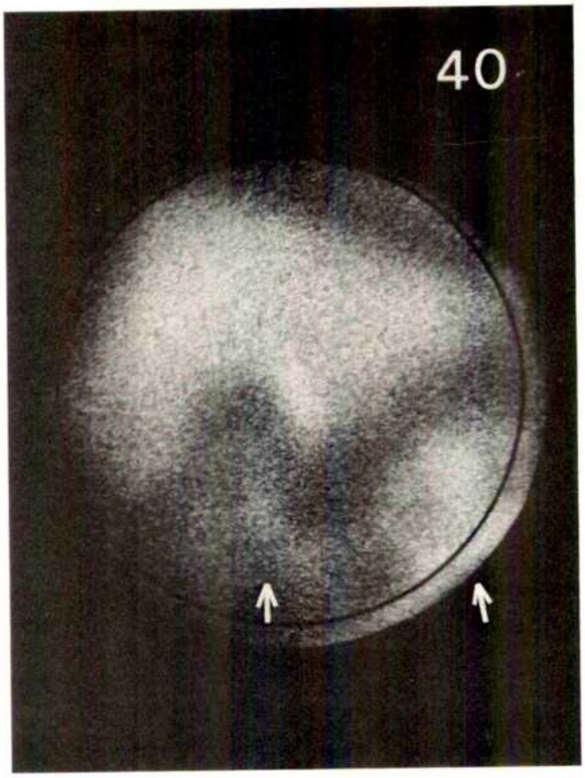


FIG. 2.

^{99}Tc^{m}-PG scan 40 minutes after injection in a patient with acute cholecystitis. The gall-bladder is not seen although the liver, bile duct, and intestines (arrowed) are demonstrated. There is a filling defect in the liver in the vicinity of the gall-bladder.

DISCUSSION

This study confirms several of our previous experimental findings. Hepatobiliary imaging with ^{99}Tc^{m}-DHT and ^{99}Tc^{m}-PG is a simple, safe and atraumatic procedure and rapid, clear biliary images can be obtained with ^{99}Tc^{m}-PG. However, neither of these radiopharmaceuticals can be recommended as a liver imaging agent. ^{99}Tc^{m}-DHT liver images were associated with background activity which became more noticeable with abnormal liver function and ^{99}Tc^{m}-PG scans were characterized by brief and sometimes uneven liver images in normal patients.

Whereas images of the gall-bladder were consistently obtained in the young pig with ^{99}Tc^{m}-PG and ^{99}Tc^{m}-DHT (Jenner *et al.*, 1976), images of the gall-bladder in apparently normal patients did not always occur. Because of possible radiation hazard our "normal" patients were all over 40 years old and they may have been a different sample from that of Matolo *et al.* (1976, 1977) in whom gall-bladder images were obtained in all 26 normal control patients. Ronai *et al.* (1975), on the other hand, found three out of ten control subjects did not show a gall-bladder image with ^{99}Tc^{m}-PG, but he was unable to confirm that these negative gall-bladder images were true or false. Although we found that ^{99}Tc^{m}-PG gave clearer biliary images than ^{99}Tc^{m}-DHT, we have documented for the first time a false-negative gall-bladder image with ^{99}Tc^{m}-PG. This could be due partly to the patient's age, but it does suggest caution in the use of ^{99}Tc^{m}-PG scans for the rapid diagnosis of acute cholecystitis. On the other hand, false-positive gall-bladder images should be rare in acute cholecystitis because cystic duct occlusion occurs in 98% of cases (Way and Dunphy, 1975). The results of Matolo *et al.* (1977) support this: they found no false-positive or false-negative gall-bladder images with ^{99}Tc^{m}-PG in 84 patients scanned for right upper quadrant pain.

Oral cholecystography is a highly specific investigation for gall-bladder disease as it can provide detail of gall-bladder size, function and contents. It therefore remains the investigation of choice when possible, but we believe there is a place for a ^{99}Tc^{m}-PG scan in the early diagnosis of *acute* cholecystitis because oral cholecystography and intravenous cholangiography are time consuming, and less reliable in the acute stage on account of the abnormal liver function which occurs in approximately 50% of cases (Raine and Gunn, 1975). Abnormal liver function probably caused the false-negative gall-bladder images in four out of five of our Group II patients and affected ^{99}Tc^{m}-DHT more than ^{99}Tc^{m}-PG. Three of these patients also had non or poorly functioning gall-bladders on oral cholecystography. Abnormal liver function, therefore, explains the close agreement we found between the biliary scan and oral cholecystography (21 out of 22 patients).

Recently there has been an increase in the frequency of gall-bladder operations (Holland and Heaton, 1972) and cholecystectomy is the most frequent major abdominal operation performed in Britain (Bouchier, 1976). There is a trend towards early operation in the management of acute calculous cholecystitis (Bouchier, 1976) and a quick, simple test such as a ^{99}Tc^{m}-PG scan would be helpful in patients for whom early surgery is contemplated. Patients who are allergic to radiological contrast materials are a group in whom a ^{99}Tc^{m}-PG scan would be more firmly indicated. Other applications include the study of abnormal bile flow *e.g.* in gastric reflux of bile, bile leaks, and internal biliary fistulae.

In conclusion, ^{99}Tc^{m}-PG is excreted rapidly into bile and gives good biliary images, though occasionally a false-negative gall-bladder image may occur. In clinical practice a ^{99}Tc^{m}-PG scan would be useful in an ill patient suspected of having acute cholecystitis as it would allow rapid diagnosis and enable surgical treatment to be planned more confidently. ^{99}Tc^{m}-DHT and ^{99}Tc^{m}-PG liver images were inferior to ^{99}Tc^{m}-sulphur colloid liver images.

ACKNOWLEDGMENTS

We thank the consultant physicians and surgeons for allowing us to study their patients, the Medical Research Council for their financial support, and the 3M Company, St. Paul, Minnesota, for supplying the DHT kits.

REFERENCES

Baker, R. J., Bellen, J. C., and Ronai, P. M., 1975. Technetium-99m-pyridoxylidene glutamate: a new hepatobiliary radiopharmaceutical. I. Experimental aspects. *Journal of Nuclear Medicine, 16*, 720–727.

Bouchier, I. A. D., 1976. Diseases of the alimentary system. *British Medical Journal, 2*, 870–872.

Eikman, E. A., Cameron, J. L., Colman, M., Natarajan, T. K., Dugal, P., and Wagner, H. R. Jr. 1975. A test for patency of the cystic duct in acute cholecystitis. *Annals of Internal Medicine, 82*, 318–322.

Holland, C., and Heaton, K. W., 1972. Increasing frequency of gall-bladder operations in the Bristol clinical area. *British Medical Journal, 3*, 672–675.

Jenner, R. E., Clarke, M. B., and Howard, E. R., 1976. Technetium-99m-dihydrothioctic acid and technetium-99m-pyridoxylidene glutamate—a study in the young pig. *British Journal of Radiology, 49*, 852–857.

Matolo, N. M., Stadalnik, R. C., Krohn, K. A., Jansholt, A., De Nardo, G. L., and Wolfman, E. F. Jr. 1976. Biliary tract scanning with ^{99m}Tc-pyridoxylidene glutamate: A new gall-bladder scanning agent. *Surgery, 80*, 317–321.

Matolo, N. M., Stadalnik, R. D., and Wolfman, E. F. Jr. 1977. Hepatobiliary scanning using ^{99m}Tc-pyridoxylidene glutamate. *The American Journal of Surgery, 133*, 116–120.

Raine, P. A. M., and Gunn, A. A., 1975. Acute cholecystitis. *British Journal of Surgery, 62*, 697–700.

Ronai, P. M., Baker, R. J., Bellen, J. C., Collins, P. J., Anderson, P. J., and Lander, H., 1975. Technetium-99m-pyridoxylidene glutamate: a new hepatobiliary radiopharmaceutical. II. Clinical aspects. *Journal of Nuclear Medicine, 16*, 728–737.

Ronai, P. M., 1975. Personal communication.

Way, L. W., and Dunphy, J. E., 1975. Biliary tract. In *Current Surgical Diagnosis and Treatment*. Eds J. E. Dunphy and L. W. Way 2nd edn. pp. 505–531 (Lange; Los Altos).

1978, *British Journal of Radiology*, *51*, 862–866

Hepatobiliary imaging: the use of ^{99}Tc^{m}-pyridoxylidene glutamate scanning in jaundiced adults and infants

By R. E. Jenner, F.R.C.S., E. R. Howard, M.S., F.R.C.S., M. B. Clarke, B.Sc., and
J. J. Barrett, M.Sc., M.R.C.P.

Departments of Surgery, Medical Physics and Nuclear Medicine, King's College Hospital, London SE5 8RX

(*Received September, 1977 and in revised form March, 1978*)

Abstract

^{99}Tc^{m}-pyridoxylidene glutamate (^{99}Tc^{m}-PG) scans have been carried out in 24 jaundiced adults (mean total bilirubin 255 μmol/l and 11 infants with prolonged obstructive jaundice (mean total bilirubin 165 μmol/l). Absence of radioactivity in the gut was interpreted as complete biliary obstruction which was the cause of jaundice in ten adults and six infants. Using this criterion occlusion or patency of the bile ducts was correctly determined in 21 adults and eight infants. False-negative gut images were found in one adult and two infants, and three scans were inconclusive (two adults, one infant). The scan was unable to show details of the site of obstruction or pathology but the technique was simple and atraumatic and was safely performed in patients with serious complications, *e.g.* renal failure, coagulation defects, septicaemia.

In infants the ^{99}Tc^{m}-PG scan compared well with the ^{131}I rose bengal faecal excretion test and with liver biopsy in the investigation of prolonged obstructive jaundice. Repeat scans in infants with biliary atresia were used to assess post-operative bile drainage. It is suggested that ^{99}Tc^{m}-PG scanning is a useful screening test in difficult cases of jaundice. It is especially useful in frail patients, and patients with complications.

Accurate diagnosis can be made in approximately 80% of jaundiced patients using standard clinical, laboratory and radiological methods (Watson, 1975). Diagnosis in the remainder is difficult but has improved with the increasing use of percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP), so that few patients should now be undergoing laparotomy for undiagnosed jaundice. The radiographs obtained from these newer techniques give good detail of the biliary tract, but these procedures are not without risk and they also require considerable expertise.

On the other hand, radioisotopic scanning is non-invasive and it offers a simple and sensitive method of assessing the function of the hepato-biliary system. Ronai's paper introducing ^{99}Tc^{m}-PG (Ronai *et al.*, 1975) is a further step towards realising these qualities with respect to gamma-camera imaging in the jaundiced patient. Our studies with ^{99}Tc^{m}-PG, initially in young pigs that had undergone excision and reconstruction of the bile ducts (Jenner *et al.*, 1976), and recently in non-jaundiced patients (Jenner *et al.*, 1978), support Ronai's and Matolo's encouraging findings (Ronai *et al.*, 1975; Matolo *et al.*, 1976, 1977). This study in jaundiced patients is concerned mainly with the ability of ^{99}Tc^{m}-PG scanning to identify adults and infants with complete biliary obstruction.

Materials and Methods

With Ethical Committee approval, 41 ^{99}Tc^{m}-PG scans were carried out in 24 jaundiced adults and 11 infants (17 ^{99}Tc^{m}-PG scans) who presented with prolonged obstructive jaundice. The ages of the adults ranged from 22 to 82 years (average 55 years), and the infants from 8 to 19 weeks (average 10.5 weeks). Half of the adults and all but one of the infants scanned had been referred from other hospitals. The mean total bilirubin values were 255 μmol/l (S.E. 28) and 164 μmol/l (S.E. 20.4) for the adults and infants respectively (normal range 3.4–20.4 μmol/l). Adults received 5–6 mCi ^{99}Tc^{m}-PG intravenously and infants an activity of 100 μCi/kg bodyweight. The preparation and analysis of ^{99}Tc^{m}-PG has just been described (Jenner *et al.*, 1978) and the percentage of free pertechnetate averaged less than 2%. Twenty-four hour urine collections were obtained from three catheterized infants and assayed using a scintillation detector for dosimetry purposes. With the exception of Case 1 (see Results) all patients were unstarved.

Early in this study patients were scanned with an early generation gamma camera, but the last 11 adults and all the infants were scanned using a new gamma camera with associated data processing facilities. The scan diagnosis was based on the presence or absence of isotope in the intestine, the latter being interpreted as complete biliary obstruction. The scans were reported independently by one of us (J.J.B.) either from Polaroid images containing 100–400 k counts or from a colour print-out obtained from the colour television display. These were usually obtained 18 hours after injection of ^{99}Tc^{m}-PG. "Early" abdominal scanning (between $\frac{1}{2}$–6 hours) was also performed in eight adults and all infants. A right lateral view was required in some instances to differentiate renal from gall-bladder images. In order to reduce possible false-negative images of the intestine, 12 adults and two infants received pancreozymin PZ (Boots) 1.5–2.0 i.u./kg simultaneously with ^{99}Tc^{m}-PG.

This dose of PZ was found to double bile flow for a few minutes after injection in the pig with division of the cystic duct (Jenner, 1976, unpublished observations). Eighteen adults underwent ^{99}Tc^{m}-sulphur colloid liver scans. Further information regarding biliary tract patency and pathology was obtained in each patient from one or more of the following:

(i) resolution of the jaundice spontaneously or with drug treatment—eight patients;
(ii) liver ultrasound—four patients;
(iii) liver biopsy—nine patients;
(iv) contrast cholangiography (PTC, ERCP)—12 patients;
(v) laparotomy—13 patients;
(vi) necropsy—four patients.

RESULTS

Tables I and II record the scan findings. No untoward reaction to ^{99}Tc^{m}-PG or PZ was observed in any patient.

TABLE I

VISUALIZATION OF THE INTESTINE WITH ^{99}Tc^{m}-PG IN JAUNDICED ADULTS AND INFANTS

Cause of jaundice	No. of patients	Intestine imaged
Adults		
Complete biliary obstruction	10	0
Hepatocellular disease*	10	9
Partial common bile duct obstruction	2	2
Sclerosing cholangitis	1†	
Hepatic metastases	1†	
Infants		
Extrahepatic biliary atresia	6	1†
Neonatal hepatitis	3	2
α_1-anti trypsin deficiency	1	0
Intrahepatic biliary hypoplasia	1	1

*8 Hepatitis, 1 drug jaundice, 1 septicaemia.
†Inconclusive result.

TABLE II

COMPARISON OF ^{99}Tc^{m}-PG SCAN WITH LIVER BIOPSY AND ^{131}I ROSE BENGAL FAECAL EXCRETION TEST IN NEONATAL JAUNDICE

	Liver biopsy	^{131}I rose bengal	^{99}Tc^{m}-PG scan
Correct	8	6	8
Incorrect	1	2	2
Equivocal	2	1	1
Total	11	9	11

Adults (24 patients)

Renal images were seen regardless of the cause of jaundice in all patients who were scanned within three hours of injection of ^{99}Tc^{m}-PG. Typically the liver images were poor compared with those seen in non-jaundiced patients (Jenner *et al.*, 1978), and the poorest hepatic uptake of ^{99}Tc^{m}-PG, and associated high background activity was seen in deeply jaundiced patients with parenchymal liver disease. Eighteen patients were also scanned after receiving ^{99}Tc^{m}-sulphur colloid which produced a clearer liver image than ^{99}Tc^{m}-PG in every case. Neither agent, however, produced liver images which were characteristic of any specific liver disease.

The ^{99}Tc^{m}-PG scan suggested 11 patients had complete biliary obstruction which was confirmed in ten (Fig. 1). Since ^{99}Tc^{m}-PG does not localize in the biliary tree in complete biliary obstruction (Ronai, 1975) it was not possible to identify the site or the

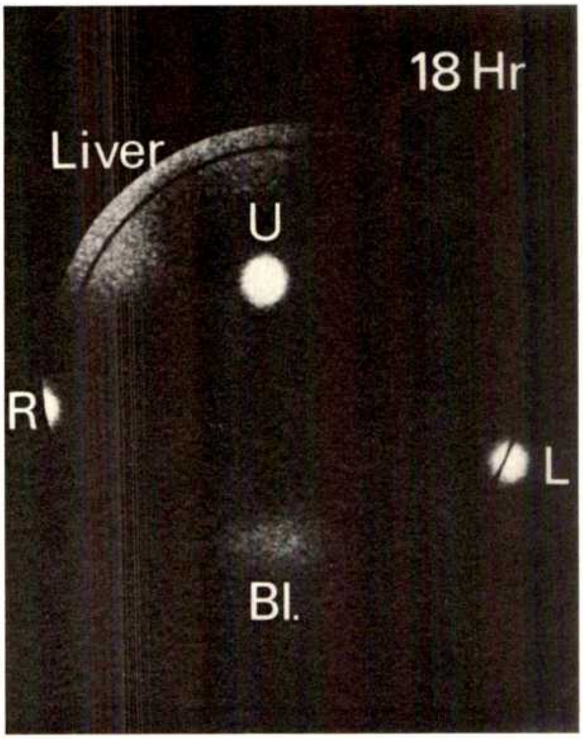


FIG. 1.

^{99}Tc^{m}-PG scan 18 hours after injection in a man who had a stone impacted in the lower end of the common bile duct. No isotope is seen in the gut suggesting complete biliary obstruction. The lower edge of the liver and urinary bladder (Bl) are the only abdominal organs seen. U, R, and L are external cobalt markers placed over the umbilicus, and right and left anterior superior iliac spines respectively.

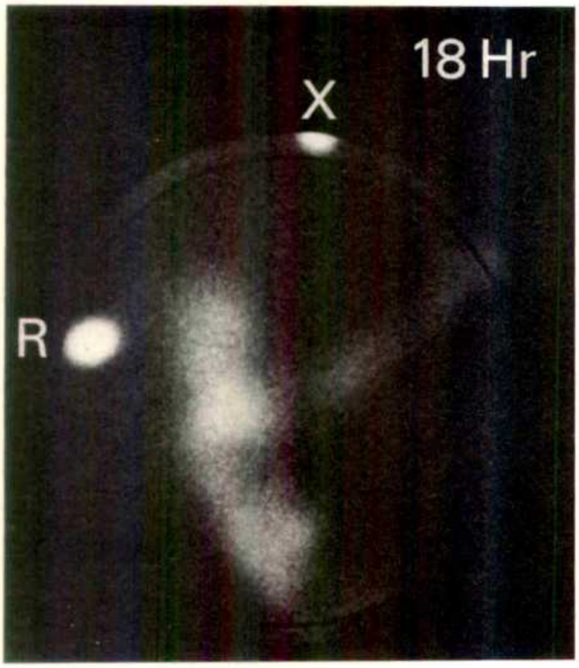


Fig. 2.

^{99}Tc^{m}-PG scan in a patient with acute relapsing hepatitis. Biliary patency is demonstrated by isotope in the ascending and transverse colon 18 hours after injection. The position of external cobalt markers over the xiphoid and lateral extremity of the right costal margin is indicated by X and R.

nature of the obstruction. One case of hepatocellular disease produced a false-negative gut image (see Table I). The value of the non-invasive ^{99}Tc^{m}-PG scan is well demonstrated in the case histories of two diabetic patients with serious complications: *Case 1* was an obese lady presenting with upper abdominal pain and jaundice which was complicated by renal failure, septicaemia and thrombocytopaenia. The ^{99}Tc^{m}-PG scan showed that the bile ducts were patent which was confirmed at necropsy one week later. *Case 2* had received an orthotopic liver graft eight months previously and was being treated with azothiaprine and steroids. Bile culture grew *Pseudomonas aeroginosa* from a permanently indwelling T-tube. Liver biopsy was consistent with hepatitis or rejection but the ^{99}Tc^{m}-PG scan and T-tube cholangiogram suggested biliary obstruction. One month later the patient died of fulminating bronchopneumonia and at necropsy biliary concretions were found obstructing the donor common bile duct.

The incorrect false-negative result referred to above was obtained from a man who became jaundiced after starting chlorpropamide four months previously. No excretion of isotope into the gut was reported, but an undilated distal biliary tract had been shown by operative cholangiography at another hospital. The total bilirubin fell steadily from 470 to 280 μmol/l during his admission, and PTC showed undilated intrahepatic ducts, thus excluding bile duct obstruction.

The 18 hour ^{99}Tc^{m}-PG scan showed evidence of bile duct patency in 11 patients (Fig. 2). Nine patients were eventually shown to have hepatocellular disease and partial bile duct obstruction was diagnosed in two. Six of the patients with hepatocellular jaundice were scanned at intervals up to six hours after injection of ^{99}Tc^{m}-PG when a gall-bladder was seen only in the least jaundiced patient (total bilirubin 88 μmol/l). Neither the gall-bladder nor the common bile duct were visualized in any of the other patients whose total bilirubin was not less than 120 μmol/l. Despite this, it should be noted that biliary patency was demonstrated in patients with severe intrahepatic cholestasis, *i.e.* total bilirubin 400–500 μmol/l.

PZ was given simultaneously with ^{99}Tc^{m}-PG to half the adults because poor quality gut images were seen in some of the first patients in the series. Eight patients in the PZ group possessed patent bile ducts and this was indicated in all of their scans, whereas only two out of four patients in the non-PZ group had an unequivocal demonstration of bile duct patency. Two Polaroid images obtained from the older generation gamma camera in patients with sclerosing cholangitis and hepatic metastases were unclear and classified as inconclusive.

More information was given by other non-nuclear investigations. *PTC* (ten patients) apart from one misleading interpretation this technique was otherwise accurate in demonstrating bile duct calibre, and the level of the pathology. *Liver biopsy interpretation* (nine patients) was correct in two out of three patients with complete biliary obstruction, and in six patients with biliary patency it led to a specific diagnosis. *Liver ultrasound* (four patients) determined bile duct calibre and the presence of gall-stones in three patients. In the fourth patient with sclerosing cholangitis the ultrasound findings were in conflict with the liver biopsy, PTC and operative findings. *ERCP* (two patients) was diagnostic on both occasions but caused pancreatitis in one.

Infants (11 patients)

Table II shows how the ^{99}Tc^{m}-PG scan compared with liver biopsy and ^{131}I rose bengal in the assessment of prolonged neonatal jaundice. Absence of isotope excretion into the gut was interpreted as biliary atresia, which was the cause of the jaundice in six infants. Possible confusion between gut and renal images at 18 hours was reduced by demonstrating the position of the kidneys at the time of the "early" scan. The biliary tract was not demonstrated during this period in any of the five infants with biliary patency. No one test was completely reliable and all three techniques had similar success rates. However, of the three investigations the ^{99}Tc^{m}-PG scan was the simplest to carry out.

Six ^{99}Tc^{m}-PG scans were performed post-operatively to monitor bile drainage in four infants with biliary atresia when agreement with clinical and biochemical indices was found on five occasions. The biological clearance of ^{99}Tc^{m}-PG in three infants was five and a half hours and the radiation dose to the kidneys was calculated to be 500 m rem which is comparable with other diagnostic investigations using ^{99}Tc^{m}.

DISCUSSION

Adults

Early and safe diagnoses are the prime objectives in the initial management of the jaundiced patient, and this paper reports our experience using a new and non-invasive technique to identify patients with complete biliary obstruction. Occlusion or patency of the biliary tract was correctly determined in 21 out of 24 adults with moderate to severe jaundice. Complete biliary obstruction was suggested by the ^{99}Tc^{m}-PG scan in 11 patients which was confirmed by laparotomy in eight patients and contrast cholangiography in two patients, whilst one patient with drug-induced jaundice was falsely diagnosed as complete biliary obstruction. These results support the findings of other workers (Ronai *et al.*, 1975; Matolo *et al.*, 1976/77; Williams *et al.*, 1977), whose collected results from 161 patients give an overall accuracy of 97% for the ^{99}Tc^{m}-PG scan in diagnosing complete obstruction.

Our slightly less accurate results may in some cases be due to the use of a less modern gamma camera, and it is likely we have scanned a more difficult group of patients. Errors and equivocal scan results did not always occur in the most deeply jaundiced patients, which suggests that failure of hepatic excretion of ^{99}Tc^{m}-PG may be related more to the nature of liver injury than to the degree of cholestasis. In an effort to reduce errors simultaneous injection of pancreozymin (PZ) appeared to enhance transit of ^{99}Tc^{m}-PG in parenchymal disease, and its administration may prevent false-negative gut images. As we have limited experience of "early" scanning we cannot confirm the results of Williams and his colleagues (1977), which suggest that hepatocellular disease can be differentiated from partial biliary obstruction.

Although ^{99}Tc^{m}-PG is a sensitive indicator of complete biliary obstruction, a clear role for its use in clinical practice has yet to emerge. This is because there are already accurate techniques available which are less invasive and give more detail. Given moderate-to-severe dilatation of the bile ducts, a combination of liver ultrasound and PTC will detect extrahepatic obstruction and also identify its level in approximately 90% of cases (Vicary *et al.*, 1977; Jain *et al.*, 1977), and it would appear little room is left for new methods of diagnosis. However, the provision of accurate and high resolution detail by these techniques and their interpretation requires considerable expertise—especially liver ultrasound where approximately 10% of examinations are unsuccessful. Conversely, ^{99}Tc^{m}-PG scanning can be carried out by a technician and gives a result in all cases which is easy to interpret. A significant complication rate is associated with PTC and ERCP but is acceptable considering the quality and quantity of information provided.

We believe that ^{99}Tc^{m}-PG scanning is a useful screening test in the "difficult" case of jaundice, when the cause of the jaundice is still uncertain after the usual clinical investigations and when the next step might be percutaneous or retrograde cholangiography. In these circumstances a ^{99}Tc^{m}-PG scan would be valuable where liver ultrasound interpretation was equivocal, unavailable or conflicted with other data, *e.g.* ^{99}Tc^{m}-s-colloid scan. The ^{99}Tc^{m}-PG scan would, therefore, be indicated in only a minority of jaundiced patients, where a functional assessment regarding biliary patency would complement the anatomical data of ultrasound. The ^{99}Tc^{m}-PG scan can be safely performed in jaundiced patients who are acutely ill with complications, *e.g.* septicaemia, renal failure and coagulation defects; and the scan may be particularly useful in ill post-operative patients—as detailed in Case 2.

Just as there have been refinements in ultrasound and PTC in recent years, new and improved hepatobiliary radiopharmaceuticals are being introduced. A compound with excellent excretion characteristics is diethyl-IDA; HIDA, a related compound, is available as an instant kit and is readily labelled with ^{99}Tc^{m}. Both compounds showed higher biliary accumulations with lower renal excretion than ^{99}Tc^{m}-PG in the normal baboon (Wistow *et al.*, 1977). A larger clinical trial than that of Ryan *et al.* (1976), comparing liver ultrasound with ^{99}Tc^{m}-diethyl-IDA (? plus PZ) might help to clarify the relative merits of these non-invasive tests in obstructive jaundice.

Infants

This is, to our knowledge, the first report of a technetium-99-labelled hepatobiliary imaging agent to diagnose infants with prolonged obstructive jaundice and to monitor post-operative bile drainage. A special problem in this age group, apart from size, is the lack of dilatation of the intrahepatic bile ducts in biliary atresia which limits the value of ultrasound and PTC. A recently published analysis of clinical and standard liver function tests in 137 jaundiced infants revealed no reliable discriminating factor in distinguishing extrahepatic biliary atresia from neonatal hepatitis (Mowat *et al.*, 1976), and in the same study percutaneous liver biopsy and ^{131}I rose bengal faecal excretion tests were the most accurate investigations. Previous animal experience led us to suggest a use for ^{99}Tc^{m}-PG in neonatal obstructive jaundice (Jenner *et al.*, 1976), and our results reported here are encouraging and compare well with these other methods of diagnosis. Defining the clinical role of ^{99}Tc^{m}-hepatobiliary imaging agents will be difficult (Ronai, 1977) but we feel a case for their use in the diagnosis and management of neonatal jaundice has been made.

ACKNOWLEDGMENT

We thank the Consultant Physicians and Surgeons for allowing us to study their patients and also the Medical Research Council for their financial support.

REFERENCES

JAIN, S., LONG, R. G., SCOTT, J., DICK, R., and SHERLOCK, S., 1977. Percutaneous transhepatic cholangiography using the "Chiba" needle—80 cases. *British Journal of Radiology*, *50*, 175–180.

JENNER, R. E., CLARKE, M. B., and HOWARD, E. R., 1976. Technetium-99m-dihydrothioctic acid and technetium-99m-pyridoxylidene glutamate—a study in the young pig. *British Journal of Radiology*, *49*, 852–857.

JENNER, R. E., HOWARD, E. R., CLARKE, M. B., and BARRETT, J. J., 1978. Hepatobiliary imaging: A comparison of ^{99}Tc^{m}-dihydrothioctic acid and ^{99}Tc^{m}-pyridoxylidene glutamate in the non-jaundiced patient. *British Journal of Radiology*, *51*, 858–861.

MATOLO, N. M., STADALNIK, R. C., KROHN, K. A., JANSHOLT, A., DE NARDO, G. L., and WOLFMAN, E. R. JR., 1976. Biliary tract scanning with ^{99m}Tc-pyridoxylidene glutamate: a new gallbladder scanning agent. *Surgery*, *80*, 317–321.

MATOLO, N. M., STADALNIK, R. C., and WOLFMAN, E. R. JR., 1977. Hepatobiliary scanning using ^{99m}Tc-pyridoxylidene glutamate. *The American Journal of Surgery*, *133*, 116–120.

MOWAT, A. P., PSACHAROPOULOS, H. T., and WILLIAMS, R., 1976. Extrahepatic biliary atresia versus neonatal hepatitis. Review of 137 prospectively investigated infants. *Archives of Diseases in Childhood*, *51*, 763–770.

RONAI, P. M., BAKER, R. J., BELLEN, J. C., COLLINS, P. J., ANDERSON, P. J., and LANDER, H., 1975. Technetium-99m-pyridoxylidene glutamate: a new hepatobiliary radiopharmaceutical. II. Clinical aspects. *Journal of Nuclear Medicine*, *16*, 728–737.

RONAI, P. M., 1977. Hepatobiliary radiopharmaceuticals: defining their clinical role will be a galling experience. *Journal of Nuclear Medicine*, *18*, 488–489.

RYAN, J., ISIKOFF, M., NAGLE, C., LOBERG, E., BUDDEMEYER, E., and COOPER, M., 1976. The combined use of Tc-99m HIDA and ultrasound in the differential diagnosis of jaundice. *Journal of Nuclear Medicine*, *17*, 545.

VICARY, F. R., CUSICK, G., SHIRLEY, I. M., and BLACKWELL, R. J., 1977. Ultrasound and jaundice. *Gut*, *18*, 161–164.

WATSON, C. G., 1975. Evaluation of the patient with suspected extrahepatic biliary obstruction. *Surgical Clinics of North America*, *55*, 419–425.

WILLIAMS, J. A. R., BAKER, R. J., WALSH, J. F., and MARION, M. A., 1977. The role of biliary scanning in the investigation of the surgically jaundiced patient. *Surgery, Gynecology and Obstetrics*, *144*, 525–530.

WISTOW, B. W., SUBRAMANIAN, G., VAN HEERTUM, R. L., HENDERSON, R. W., GAGNE, G. M., HALL, R. C., and MCAFEE, J., 1977. An evaluation of ^{99m}Tc-labelled hepatobiliary agents. *Journal of Nuclear Medicine*, *18*, 455–461.

Book review

Tomodensitométrie Cranio-cérébrale (*Scanographie*). Edited by A. Wackenheim and E. Babin, pp. xii+254, 317 figs., 1978 (Paris, Editions Masson), F.220.

It is not clear from the cover that this book on CT scanning is in fact a multi-author product; in addition to the two editors and the writer of the preface, Professor Gros, there are 15 other authors, although only 13 are included in the list of contributors.

The main interest of the book lies not so much in the overly brief clinical sections—the chapter on glial tumours consists of less than two pages of text and five figures, for example—but in the extensive and comprehensive treatment of technical aspects, which forms more than 40% of the text. For this, the editors were fortunate in having a close collaboration with two workers from CGR, one of whom, M. Krausz, has provided one of the best accounts of the principles and functions of the CT scanner I have come across.

All the CT pictures in the clinical chapters were obtained with the original model of the CGR Densitome. There is considerable emphasis on analysis of attenuation coefficients, which is of course a facility of this apparatus; this is likely to seem less important in the future, given the improved picture quality of present-day machines and of those yet to come.

The authors provide an extensive chapter-by-chapter bibliography, and suggest a system of scan classification upon which readers may care to base their own. French-speaking radiologists will perhaps find it interesting to have a Gallic viewpoint on a now-familiar subject: Professor Gros, for example, mentions French forerunners of both Röntgen and Hounsfield. The final Franglais glossary of CT terms should aid in this respect.

I. F. MOSELEY.

Constancy of radiation output during diagnostic X-ray exposures

By G. M. Ardran, M.D., F.R.C.P., F.R.C.R., H. E. Crooks, F.C.R. and R. Birch, M.Sc., B.Sc.

Environmental and Medical Sciences Division, A.E.R.E., Harwell, Didcot, Oxon., and the Department of Radiology, University of Oxford

(*Received November, 1977 and in revised form March, 1978*)

ABSTRACT

Variation in X-ray output and quality during a diagnostic exposure can be undesirable and may result in unnecessary dose to the patient. When significant build-up or decay periods are present errors will arise if factors obtained under steady-state conditions are employed to estimate the exposure. These parameters must be taken into account when calibrating X-ray generators.

A variable speed spinning film device and a spectrometry system have been used to measure the variations under fluoroscopic and radiographic conditions for a number of generators. Variations in output due to filament heating, voltage supply and rectification, cable capacity and target pitting have been demonstrated. At low fluoroscopic currents, large surges and long decays have been observed; the significance of these effects is considered.

The X-ray output during a diagnostic exposure should ideally be constant in quantity and quality, but in practice it varies considerably depending on the type of voltage supply, rectification and the current and voltage settings used. During fluoroscopy there may be an initial build-up or surge with some generators which could result in unnecessary dose to the patient. When we first used closed circuit television in 1961, we noticed that when the fluoroscopic circuit was broken the radiation persisted and decayed slowly due to cable capacitance, the effect being greatest at low currents. This has also been noted by Cole (1976). These build-up and decay periods must be taken into consideration when calibrating an X-ray generator, for example in the estimation of tube voltage and X-ray quality using a penetrameter cassette (Ardran and Crooks, 1968), especially if exposure times are short. In some circumstances it is advisable to eliminate these factors by the use of a lead shutter (Ardran and Crooks, 1978). Errors may also arise if factors obtained under steady-state conditions, or for different exposure times, are used to estimate the exposure during intermittent fluoroscopy when the total exposure time has been recorded.

In the past, some of these parameters have been investigated by spinning tops (sometimes motorized) (Kemp, 1946; Ardran and Crooks, 1974; Saito *et al.*, 1975), fast reading ionization chambers (Greening, 1959), solid state detectors (Higgins, *et al.*, 1967) and intensifying screens observed by a photomultiplier (Taylor, 1975). The purpose of this paper is to describe some results obtained with an improved spinning film device and with a Ge (Li) detector. These devices have demonstrated build-up surges and decay with fluoroscopy circuits. Other inconsistent outputs have been detected which we attribute to a combination of causes. These will be discussed.

METHODS AND EQUIPMENT

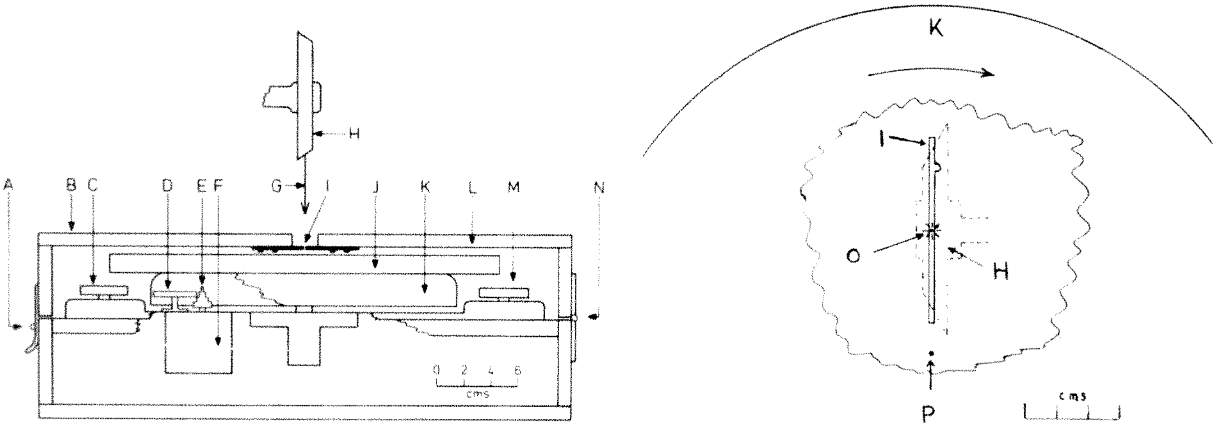
Spinning film device

The spinning film device consists of a record-player turntable, powered by a synchronous motor, which provides four speeds of rotation without gear hunting (see Fig. 1A). The cassette on the turntable is exposed through a slit 0.3 mm × 60 mm in the lead-covered lid, aligned along a radius of the turntable such that the central beam is centred over the middle of the slit (see Fig. 1 B). The slit is 5 mm from the film and its length should correspond with the plane at right angles to the long axis of the tube to prevent off-focus radiation fogging areas adjacent to the instantaneous slit image. In order to recognize the beginning of each exposure, the slit is enlarged towards the end furthest from the point of rotation, with a semi-circular hole 3 mm in diameter (Fig. 1B); this will appear in advance of the slit exposures and, being more heavily exposed, will record very low intensities not readily detectable through the slit. A moving film rather than a moving aperture ensures that the central beam is used and heel effect avoided.

With the range of speeds of rotation of 16, 33, 45 and 78 r.p.m. (equal to 0.77, 1.33, 1.82, 3.75 sec per revolution), the various speeds of intensifying screen available, and use of different focal distances, the output under both high and low current conditions can be studied. The fastest screens (rare earth) have enabled measurements to be made at very low currents.

Spectrometry to measure photon output

The collimating system used is a shortened version of that reported by Peaple and Burt (1969), and consists basically of three lead collimators, set at known distances apart, permitting only a narrow beam of radiation to hit the detector. The detector was a Ge (Li) planar crystal, 10 mm diameter by



A Fig. 1. B

(A) Schematic diagram of the spinning film device. (B) Plan view showing aperture and its relation to centre of turntable and X-ray focus.

A. Clip to ensure register of lid; B. 2.00 mm lead facing with 2 × 12 cm aperture; C. Speed selector; D. Rubber wheel transmitting drive from spindle to turntable; E. Spindle with different diameters to select speed changes; F. Synchronous motor; G. Central ray; H. Rotating anode; I. 0.3 mm × 6.0 cm aperture in 2.0 mm lead mounted on 1.0 mm brass showing position of 3.0 mm indentation (aperture width not to scale); J. Film cassette; K. Turntable with clockwise movement; L. Plywood case; M. On-off switch; N. Lid hinge; O. X-ray focus; P. Centre of turntable.

8 mm deep, having a gold surface layer of thickness 0.04 μm. The system used to measure the variation in photon output with time consists of a single-channel analyser which converts the pulses of various heights received from the detector into uniform pulses that are stored in a Geoscience 1024 channel digital processor (Birch, *et al.*, 1976). In the multiscale mode the multi-channel processor records the number of pulses received during 1024 successive chosen time intervals. To measure the variation in photon output over several seconds a 6 ms time interval per channel is chosen whereas to observe the variation in output due to voltage and current ripple a shorter time interval of 50 μs is used. The data are then corrected for dead time, which is the period (5 μs in this case) following each count when the detecting system is insensitive to further incoming photons.

An estimation of the variation in beam quality with time was made by repeating the measurements with increasing copper filtration. Any variation in photon output, relative to the steady-state condition, between the different filtrations is an indication that the quality of the beam is altering. Previously measured spectra (Marshall *et al.*, 1975) can then be corrected for filtration to produce the same reduction in photon flux, thereby giving the instantaneous voltage across the tube. This technique is being further refined and will be published.

Temperature of X-ray tube filament

The tube current is determined by the number of electrons given off due to thermionic emission from the hot cathode. The light emitted from the heated cathode will also vary with tube current, although for a given change in temperature the change in electron output has been calculated to be approximately six times greater than that of the light output (Marshall, 1977). The variation in light output during an exposure was observed using a fibre optic device and also a silicon photocell. The voltage from the photocell, which is proportional to the light incident upon it, can be displayed on an oscilloscope. The effect of X rays on the photocell was determined by inserting a piece of black paper between it and the filament, and was found to be insignificant.

The effect of pulsed filament current had been observed previously when using a condenser discharge generator (Crooks *et al.*, 1971).

Results

(1) *G. R. Heliophos—Full wave rectified, single-phase generator.*

(a) *Radiography*

Figure 2A shows a typical spinning film obtained for radiographic conditions (90 kV, 100mA) showing a large amount of ripple on the output. There is no noticeable build-up or decay.

(b) *Fluoroscopy*

In contrast Fig. 2B shows the output variation at 1.0 mA with a long build-up reaching a fairly constant output after approximtaely two seconds. Note that the time for one revolution of the film in

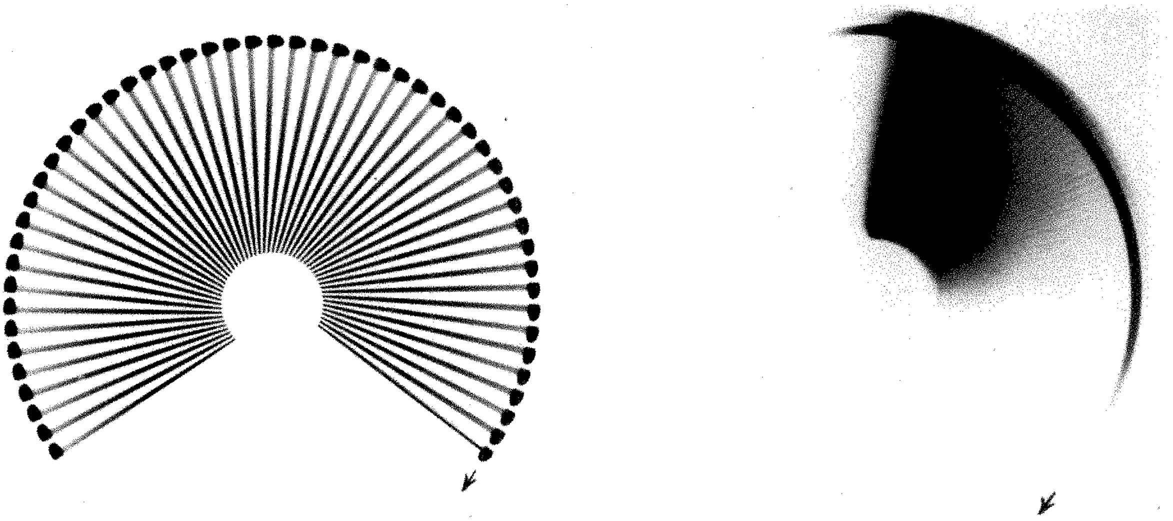


FIG. 2.
Output variation from a full-wave rectified, single phase generator (G. R. Heliophos) at (A) 90 kV, 100 mA, 0.77 sec per revolution. (B) 90 kV, 1.0 mA, 3.75 sec per revolution.

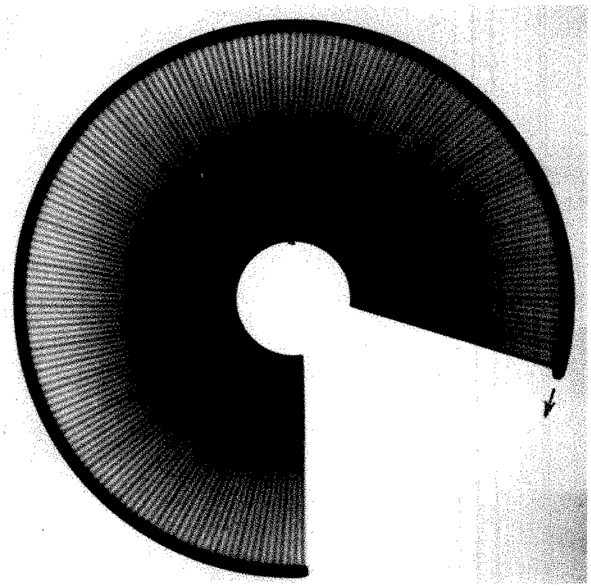


FIG. 3.
Output variation under radiographic conditions (60 kV 100 mA) for the Philips Maximus DLX, three-phase, six peak generator. Speed of rotation of film: 0.77 sec per revolution.

Fig. 2A was 0.77 sec whereas in Fig. 2B it was 3.75 sec. In this equipment under fluoroscopic conditions the filament is not pre-heated and gradually builds up to the correct temperature. This was confirmed using a fibre-optic device. At the end of the exposure a small amount of radiation continued to be emitted for about 0.25 sec due to cable capacitance.

(2) *Philips Maximus DLX generator*

(a) *Radiography*

The Philips Maximus DLX generator has a three-phase supply giving six peaks per mains cycle under radiographic conditions.

The output variation at 60 kV, 100 mA is shown in Fig. 3. It can be seen that every third and sixth pulse is more intense. Spectrometry has indicated that this is due to a combination of current ripple, caused by a.c. filament heating, and the voltages of the three phases being different; voltmeters connected to the three phases have shown large variations throughout the day. A typical set of voltage readings over an average working day is given in Fig. 4.

(b) *Fluoroscopy*

For fluoroscopy the generator operates from only one phase (two peaks). A long decay period was observed using spectrometry and the results are shown in Fig. 5. At very low currents (0.2 mA) X rays were still being emitted for up to ten seconds after the termination of the exposure. This is a result of the slow decay of tube voltage due to cable capacitance. In order to calculate the exposure to the patient during the decay period relative to that in the steady state, a knowledge of the variation in tube voltage is required. The instantaneous voltage at various times during the decay was estimated from measurements repeated with different amounts of copper filtration, as described earlier. The data were then divided in sequential 5 kV blocks to enable the calculation of the relative exposure. The results are

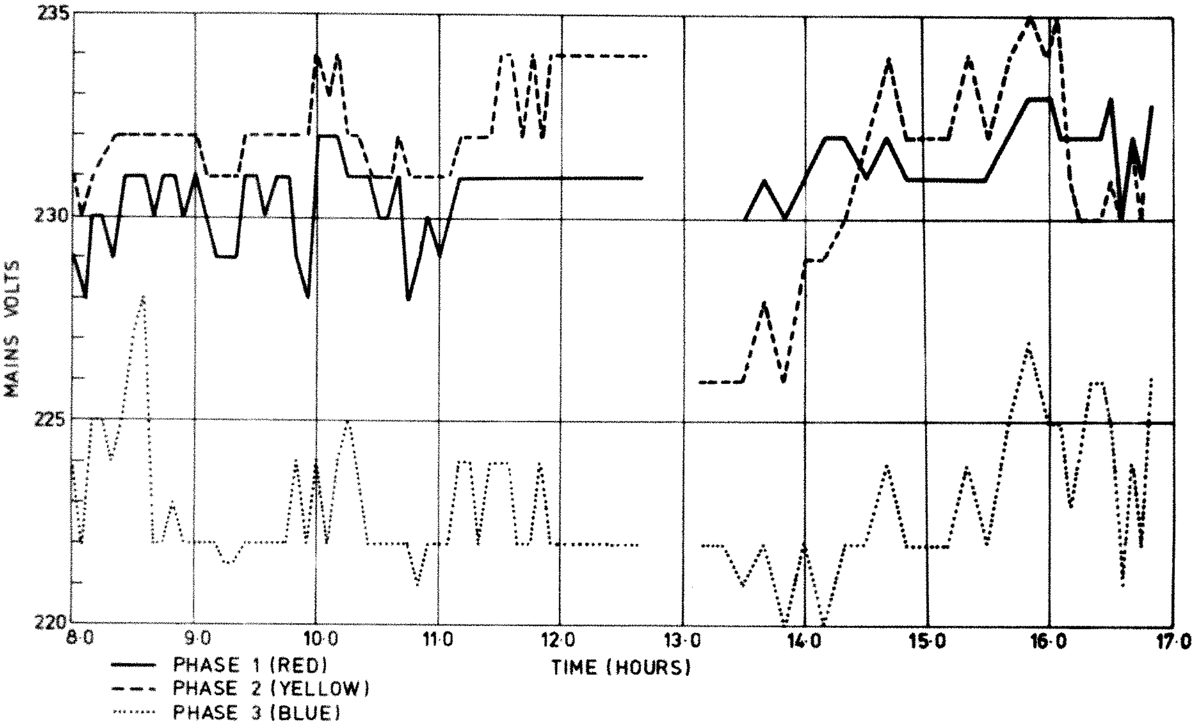


Fig. 4.

Voltages observed on our three phase mains supply recorded at intervals of five or ten minutes from 0800 to 1700 hr with a short gap during the lunch break. These voltages are fairly typical of those found from day to day.

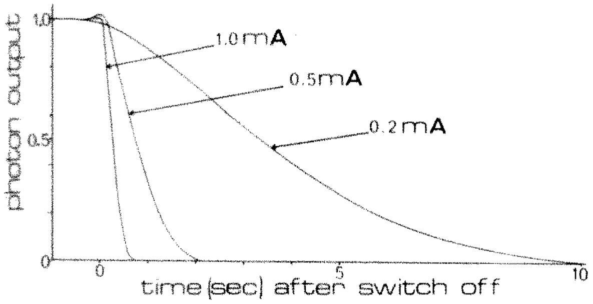


Fig. 5.

Decay of photon output for Philips Maximus DLX at 98 kV, inherent filtration (0.8 mm Al) for three currents: 0.2 mA, 0.5 mA, and 1.0 mA, normalized to give an output of 1.0 during the steady state.

TABLE I

Exposure during the decay period expressed as a percentage of the exposure during a 10 sec exposure (*i.e.* 10 sec between switch on and switch off)

	Tube current (mA)	kV	Total filtration	Percentage of 10 sec exposure
(a) Philips Maximus DLX	0.2	98	Inherent (0.8 mm Al)	46.0
	0.5	98	Inherent (0.8 mm Al)	8.3
	0.2	98	2.5 mm Al	39.0
	0.5	98	2.5 mm Al	7.0
	0.2	98	1.5 mm Cu	12.0
	0.5	98	1.5 mm Cu	4.0
(b) Siemens Gigantos (Smoothed Circuit)	0.1	90	Inherent (0.62 mm Al)	10.8
	0.2	90	Inherent (0.62 mm Al)	5.9
	0.4	90	Inherent (0.62 mm Al)	4.4

shown in Table I for different filtrations and tube currents. The filament current was adjusted prior to the exposure and remained the same before, during and after the exposure. Measurements with the spinning film device showed pulsing during the decay due to a.c. filament heating. If the equipment is switched off by disconnecting the mains supply during the decay, the X rays immediately terminate, but are again produced if the mains supply is reconnected up to two minutes afterwards. This reheats the filament and pulsing is distinctly seen without switching on the high voltage.

(3) *Siemens Gigantos generator.*

(a) *Radiography*

The Gigantos generator has a three-phase supply giving 12 peaks per mains cycle. The output variation at 24 kV, 190 mA is shown in Fig. 6. The twelve peaks of the voltage ripple are visible, but there is also a variation at fifty peaks per second superimposed on this. This cannot be due to current ripple as it occurs at only half the required frequency and it is therefore attributed to some imbalance in the rectifying circuits.

(b) *Fluoroscopy* (smoothed circuit)

The generator can be operated at low currents for fluoroscopy from a single phase of the supply (two peaks). The circuit has been modified by the addition of a large condenser to provide additional smoothing, giving 0.5% voltage ripple at 1 mA 100kV.

The photon output under fluoroscopic conditions was examined by spectrometry (Fig. 7B) and by the spinning film apparatus (Fig. 8). The results depicted show an initial burst at high intensity (shown dashed in Fig. 7B) reducing to zero after 0.03 sec. This can only be caused by a voltage surge since no corresponding surge was seen in the filament temperature. This is followed by a surge in photon output which gradually reduces to the steady state value. By repeating the measurement with increasing copper filtration an estimate of the instantaneous tube voltage was made. The times after switching on when the voltage reached 87 and 90 kV are marked in Fig. 7B. Since the tube voltage rapidly reached its set value the photon output during the initial surge and steady state can be assumed to be proportional to the exposure rate.

The large surges in photon output can be explained by the variation in filament heating during the exposure. The photon output is proportional to the filament temperature which has been estimated, as described earlier, by measuring the light output from the filament. The Siemens Gigantos generator has a "pre-heat" on the filament and it can be seen in Fig. 7A that at low tube currents (less than 2.0 mA) the filament temperature slowly falls, after the start

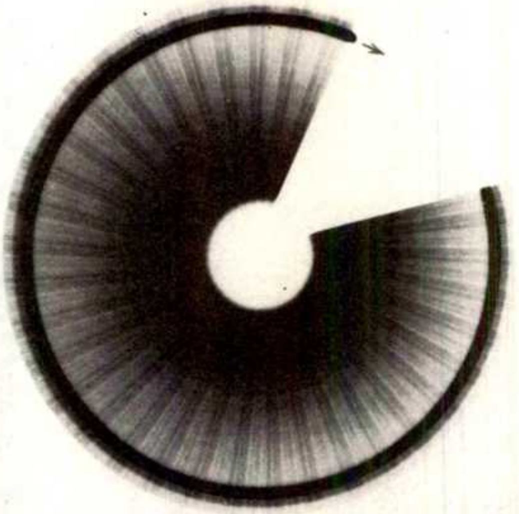


FIG. 6.

Output variation from Siemens Gigantos generator at 24 kV, 190 mA, inherent filtration (0.62 mm Al), showing voltage ripple (0.77 sec per revolution). The variations due to imbalance in the phases were clearly shown at 80 kV but each individual pulse was less clearly seen because of low contrast and the inherent unsharpness of intensifying screens at this energy. This film taken at low voltage was chosen for clarity of illustration.

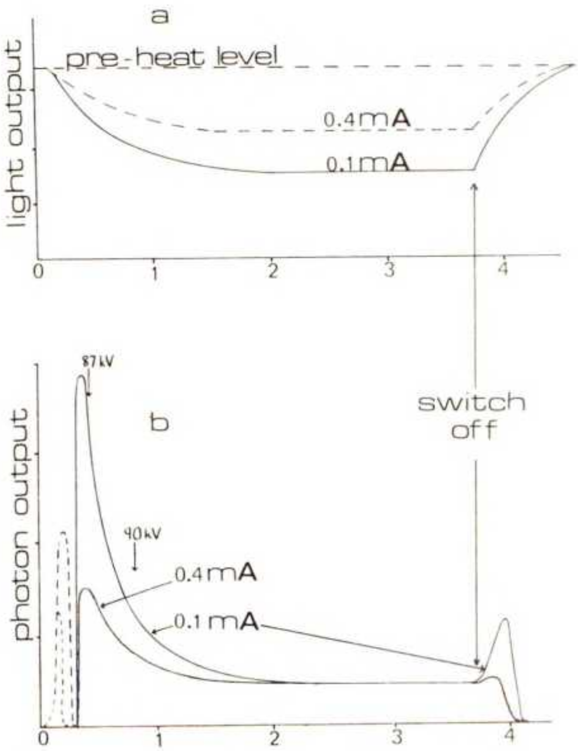


FIG. 7.

(a) Variation in light output from filament with time at 90 kV with tube currents of 0.1 mA and 0.4 mA, for Siemens Gigantos generator.

(b) Variation in photon output with time at 90 kV, 0.1 mA and 0.4 mA (inherent filtration), normalized to a value of 1.0 during steady state.

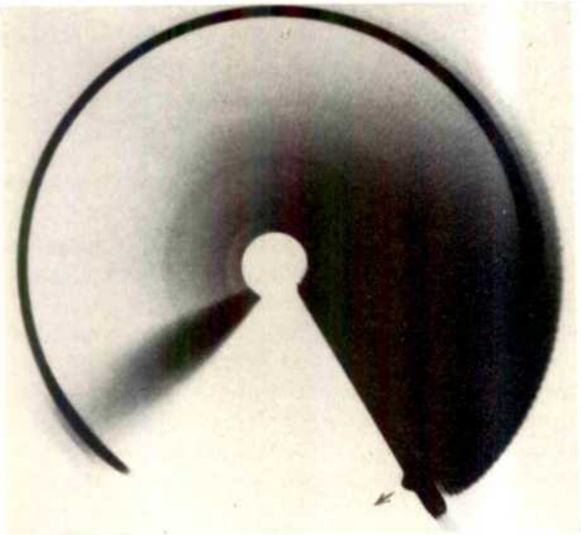


FIG. 8.

Output variation from the Siemens Gigantos generator for the circuit with a large smoothing condenser added, at 90 kV with 0.62 mm Al equivalent inherent filtration for tube current of 0.1 mA.

of the exposure, to its steady state value. The effect of this on photon output is shown in Fig. 7B. When the voltage is applied to the tube the output quickly reaches a maximum (ignoring the dashed region) since the filament temperature is still near to its "pre-heat" temperature. As the filament temperature falls to its steady state value there is a corresponding fall in the photon output.

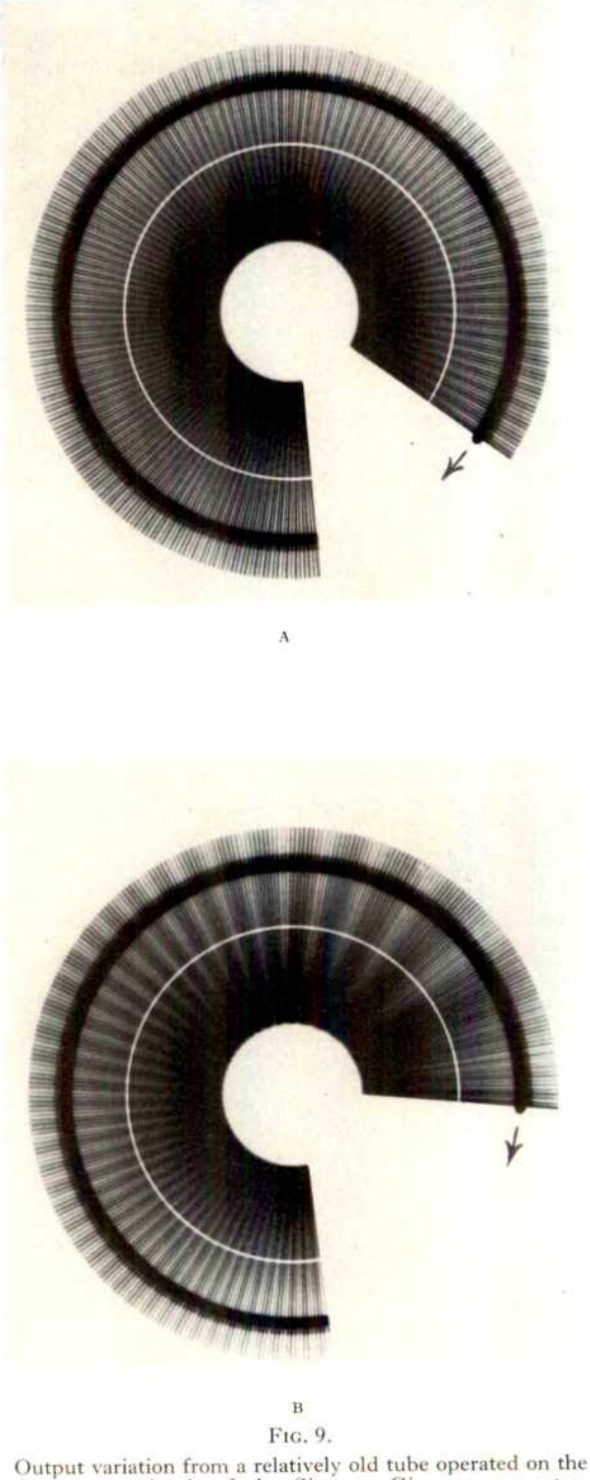
When the exposure is terminated there is another surge in photon output, before the output finally decays away due to reduction in tube voltage. This surge is due to the filament temperature rising, after the termination of the exposure, to its "pre-heat" value.

As the set tube current is increased from 0.1 mA the surges in output reduce in magnitude until at 2.0 mA no surges are present. At this current there is no change in filament temperature during the exposure.

(c) *Fluoroscopy* (unsmoothed circuit)

A relatively old tube is also operated on the conventional fluoroscopy circuit of the Gigantos generator without the large smoothing condenser. The results were similar to the tube operating from the smoothed circuit except that it did not have the initial high intensity burst (shown dashed in Fig. 7B).

The spinning film results (Fig. 9) show that each peak was not of the same intensity and that periodically there were fairly distinct white lines instead of black or grey lines. The appearances of these



A

B

FIG. 9.

Output variation from a relatively old tube operated on the fluoroscopy circuit of the Siemens Gigantos generator, showing target roughening. 80 kV, 4.0 mA; 3.75 sec per revolution; inherent filtration 1.0 mm Al equivalent. (A) with anode commencing rotation. (B) with anode at full speed.

variations changed if an exposure was made simultaneously with the anode commencing rotation (Fig. 9A) or at the full speed (800 r.p.m.) for fluoroscopy (Fig. 9B). No variations in speed of rotation of the film could be demonstrated using a three-phase light source. With a two pulse circuit these variations could not be due to the effects of filament heating or to variations in voltage of individual phases of three-phase supply. By a process of elimination this was considered to be due to target roughening or pitting. Examination of the target through the tube port indicated that this was roughened over the whole target area and with some small pits. It would be advantageous to rotate the anode at a slower speed by reducing the voltage applied to the rotating anode, or use low current to produce nearly constant potential, when discontinuities in the image would indicate target pitting. At full speed the anode of this tube rotates fifty times during one revolution of the film for the conditions used in Fig. 9B (3.75 sec per revolution).

Variation in output of X-ray generators

Many repeat exposures were made using the Siemens, Philips and General Radiological equipments described above, together with a self-rectified dental generator. The variations in output were ±9%, ±16%, ±10% and ±15% respectively. When these observations were repeated during the lunch break when the mains voltage remained fairly constant, the output variations were reduced to a few per cent.

When repeat exposures were made it was often found that if the minimum preparation time was used the output was lower than if the preparation time was prolonged by 1 to 5 sec over the minimum permitted by the equipment. With the minimum preparation time outputs could be reduced by up to 20%. If the effective kV was measured using a penetrameter cassette, it was found that when the output was reduced following minimum preparation time, the kV recorded was frequently high by about 2 kV. This, we presume, was due to the power load on the transformer resulting from the tube filament not yet having reached its stable temperature. With generators without filament pre-heat, *e.g.* self-rectified dental generators, the kV is higher during the initial heating period than when stable conditions are established and may be up to 6 kV higher.

DISCUSSION

Under radiographic conditions no surges or decay periods have been observed. Large variations due to voltage ripple have been shown, and also variations in output due to the voltages of the three phases of the mains supply being different. The exposure obtained for given settings on the tube may vary from exposure to exposure depending upon the type of mains compensation employed with the generator. The Philips generator has compensation derived from two of the phases whereas the Siemens Gigantos has compensation derived from only one. It would therefore be expected that variations due to relative changes in the three voltages of the three phase supply should be smaller for the Philips generator.

The initial surge and decay period during fluoroscopy at low currents could be of importance when a large number of short exposures are made. They may then account for a significant proportion of the dose received by the patient, which may not be appreciated if fluoroscopic times and outputs measured under constant conditions are employed to estimate the dose. It must be emphasized that these effects are not found in all generators. It would seem that a system where the filament current is set prior to the exposure is more desirable than one where there is a pre-heat level which adjusts once the exposure has commenced, since in the former case all surges due to varying filament current are removed. There may well be good design reasons for having the pre-heat type of system; if this is the case, the pre-heat level should be set to the lowest value that is likely to be used. Alternatively, where surges and decay periods are present, a shutter, timed to open when the output is stabilized and close before the end of the exposure, would reduce unnecessary dose to the patient.

The spinning film has proved a useful device for examining output variations during diagnostic exposures, showing surges and decay, imbalance between rectifiers, variations due to a combination of voltage and current ripple, and target pitting. Spectrometry has provided additional information on the variation in photon output and the variation in quality. The measurement of voltages on a three phase mains supply is not readily carried out since voltmeters have to be wired in. It is also not easy to record the voltages over a period of time since this requires a great deal of manpower and automatic voltage recording systems are not readily available for long periods of time.

ACKNOWLEDGMENTS

This work was partly supported by the Biology Division of Euratom (Contract No. 245/77.1 B10 UK). The authors would like to thank Mr. E. Renel of Philips Medical Systems for assistance and advice, and Dr. M. Marshall for useful discussions throughout this work.

REFERENCES

Ardran, G. M., and Crooks, H. E., 1968. Checking diagnostic X-ray beam quality. *British Journal of Radiology*, *41*, 193–198.

1974. Field emission 350 kVp chest X-ray system. *Radiography*, *40*, 277–284.

1978. Penetrameter cassette calibration to 400 kV: effects of extra focal radiation when measuring tube filtration. *British Journal of Radiology*, *51*, 29–34.

Birch, R., Marshall, M., and Peaple, L. H. J., 1976. A technique for measuring the variation of photon spectrum from X-ray generators over the mains voltage cycle. *Physics in Medicine and Biology*, *21*, 745–753.

Cole, J. G. L., 1976. Private communication.

Crooks, H. E., Sangster, J., Twemlow, S., and Ardran, G. M., 1971. A capacitor discharge mobile X-ray generator. *Radiography*, *37*, 105–111.

Greening, J. R., 1959. Testing X-ray equipment by examining emitted X-rays. *Radiography*, *25*, 199–210.

Higgins, E. M., Rosenbaum, H. D., and Devore, W. D., 1967. Radiation beam analyser for diagnostic radiology. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *101*, (4), 983–987.

Kemp, L. A. W., 1946. The physicist in the radiographic department. *British Journal of Radiology*, *19*, 304–313.

Marshall, M., Peaple, L. H. J., Ardran, G. M., and Crooks, H. E., 1975. A comparison of X-ray spectra and outputs from molybdenum and tungsten targets. *British Journal of Radiology*, *48*, 31–39.

Marshall, M., 1977. Private communication.

Peaple, L. H. J., and Burt, A. K., 1969. The measurement of spectra from X-ray machines. *Physics in Medicine and Biology*, *14*, 73–85.

Saito, K., Kanda, K., and Aoyagi, T., 1975. High tension phenomena analysed by strobo patterns with a newly developed X-ray strobo-scope. *Japanese Journal of Radiological Technology*, *31*, 93–99.

Taylor, K. W., 1975. Quality control in a large teaching hospital. *SPIE*, 70, Medicine IV.

Book review

Xeroradiography in Otorhinolaryngology. L. Di Guglielmo, R. Campani, P. Garbagna, and E. Mira, pp. 187, 1977. (Excerpta Medica, Amsterdam, Oxford) $108.75/D.fl.250.00.

The powder development of an electrostatic image produced by X rays was first described in 1903 by Righi and like many another good idea has since been looking for a suitable application. Some of the earlier disadvantages have recently been overcome by the availability of a commercial method of charging plates and producing pictures from these, and this new impetus has created fresh interest in the technique.

The authors of this bilingual book, produced with one English and one Italian column of print on each page, state in their introduction that they have been using xerography in the field of otorhinolaryngology since 1974 and that their book is intended to be a critical review of their material. The book is divided into major sections which cover the pharynx, larynx, trachea, nasal cavities, and other applications of the xeroradiographic technique in the soft tissues of the neck, the tempero-mandibular joint, lateral cephalometry and field size in radiotherapy. Each section has a few pages of introduction in which the authors discuss the material, the features shown on the xerograms, the pathology found and their technique for examining the area. These pages are related to the illustrations which follow the introductory section so that one has to keep turning forwards to look at the figures referred to in the introduction. The references at the end of each section include all the recent relevant material published on xeroradiography. In spite of the title there is no section on the ear.

The majority of the illustrations are magnificent and provide representative examples of the lesions found in each area. The English translation is for the most part idiomatic, but the various sections have presumably had different translators since that on the trachea shows its Italian origin quite clearly without detracting from its intelligibility. The production overall is excellent and the number of spelling mistakes is insignificant.

The authors end by giving their conclusions with a list of the relevant advantages and disadvantages of xerography and conventional radiography. However, they leave out of the list of disadvantages the production of artefacts which often spoil xerograms, and that of cost. On p. 129 they say that in the examination of the paranasal sinuses the results of xeroradiography were not significantly better than those of conventional radiography, so that xerotomography was usually done; and yet in the final conclusions they state "this comparison yielded the same results in all branches of otorhinolaryngology, namely that xeroradiography and xerotomography give better results". There seems to be some disagreement here. The recurrent statement in publications on xeroradiography that more detail can be seen on xerograms needs to be properly tested, and it is unfortunate that the authors of this book have not given the reader any factual results from the critical review of their material.

There is no doubt that this guide illustrates elegantly some of the more common radiological abnormalities met with in the areas of the nose and throat and those departments doing ENT work and considering the use of xeroradiography should contemplate buying this book. Should supplies of silver become difficult we shall probably all be glad to use xeroradiography, but I am not yet convinced that the technique is in fact superior to good quality radiography.

W. D. Jeans.

1978, *British Journal of Radiology*, *51*, 875

Hyperbaric oxygen and radiotherapy.

The Medical Research Council's Working Party

By Sir Brian Windeyer, F.R.C.P., F.R.C.S., F.R.C.R.
Moreton Gap, Thame Park Road, Thame, OX9 3PP

(Received April, 1978)

ABSTRACT

Randomized controlled clinical trials in a number of tumour sites have been co-ordinated by the working party and have now reached the stage of publication. As a result of the co-operative effort, results of importance have been achieved.

This report of the Medical Research Council working party on Radiotherapy and Hyperbaric Oxygen may appear to be long delayed as it is 15 years since the group was established. There were, however, many difficulties in devising and carrying out a clinical trial, with adequate controls, of a method of treatment of malignant disease involving a number of sites.

The hyperbaric oxygen chamber had been used for some years in a few radiotherapy centres. It required an exacting and time-consuming technique. Relatively few patients could be treated in a day and it was obvious that to obtain adequate numbers it would be necessary to have the collaboration of as many radiotherapy departments as possible.

Some workers were already convinced of the benefits of treatment with hyperbaric oxygen and believed that any patient who appeared suitable should be given the benefit of this treatment. They considered that it would not be ethical to make a random selection of some of them for any form of treatment. Many considered that any new and hitherto unproven method should not be used for the treatment of patients who had some chance of cure by more orthodox methods, and were only willing to submit the most advanced cases for such a trial. It is more difficult to eliminate extensive primary disease and such patients have no great likelihood of prolonged survival because of persistence of the primary lesion or the likelihood of development of metastases. It was, however, necessary to use both longevity and local elimination of disease as the criteria of successful treatment.

When the trials got under way with the collaboration of various centres it was not found to be appropriate to have the same detailed technique used by all centres, as there could not be complete agreement on such matters as protraction, fractionation and dosage. It was, however, agreed that each centre would adopt exactly the same details of technique for their patients treated in hyperbaric oxygen as for their control patients treated in air.

Gradually the pooling of experience brought mutual recognition that the hyperbaric oxygen patients might need a different type of fractionation and protraction from that most suitable for patients treated in air and so the protocol had to be changed and greater liberty given to each centre, particularly with regard to the techniques to be used for the control series.

Because of the various essential changes in protocol and the differences in technique at each centre it would not have been possible to bring the trials to a close at an earlier date and show any meaningful results. The results are being reported now not because the trials have come to any natural termination but because the working group considered that enough had been done at this stage to give a reasonable picture of the present state of knowledge of radiotherapy with hyperbaric oxygen. There is still much work to be done and more to be learned, particularly with regard to fractionation, protraction and dosage.

The results produced so far are a tribute to the enthusiasm and hard work of the participants in each centre. It is difficult to maintain the impetus in an investigation such as this lasting over 15 years but the participants have worked even closer together as the years have gone by.

Perhaps of equal importance to the statistical results presented has been the demonstration that controlled clinical trials of methods of treatment of cancer can be conducted by collaboration between centres not only scattered throughout this country but also with participation of centres abroad.

Reprints of the MRC working party reports (*BJR*, *51*, 875–894) are available free on application to the Managing Editor, British Journal of Radiology, 32 Welbeck Street, London W1M 7PG (send large stamped addressed envelope).

1978, *British Journal of Radiology*, *51*, 876–878

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the bladder

By I. S. Cade, M.S., F.R.C.S., F.R.C.R. and J. B. McEwen, M.B., F.R.C.R.,
Department of Radiotherapy and Oncology, St. Mary's General Hospital, Portsmouth PO3 6AD
S. Dische, M.D., F.R.C.R., and M. I. Saunders, M.B., F.R.C.R.,
Marie Curie Research Wing for Oncology, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN
E. R. Watson, M.B., F.R.C.R., and K. E. Halnan, F.R.C.P., F.R.C.R., F.R.S.E.,
Glasgow Institute of Radiotherapeutics, Western Infirmary, Glasgow G11 6NT
G. Wiernik, M.D., F.R.C.R., and D. J. D. Perrins, M.D., F.R.C.S.,
Research Institute, The Churchill Hospital, Headington, Oxford OX3 7LJ
and I. Sutherland, M.A., D.Phil.
MRC Statistical Research and Services Unit, University College Hospital Medical School, 115 Gower Street, London WC1E 6AS

(*Received April, 1978*)

Abstract

In a randomized controlled clinical trial of hyperbaric oxygen in the radiotherapy of carcinoma of the bladder a total of 241 cases were contributed by four radiotherapy centres in the United Kingdom. In this trial where in each centre identical radiotherapy was employed for both oxygen and air cases, no benefit was shown with the use of hyperbaric oxygen.

During the past 20 years patients with carcinoma of the bladder have received treatment in hyperbaric oxygen in an effort to demonstrate a process of radiosensitization by this method of treatment. For patients with advanced carcinoma of the bladder radiotherapy is probably the best method of radical treatment available, but five-year survival rates are only of the order of 30%, indicating that there is an urgent need to improve the method of treatment. The working party on radiotherapy and hyperbaric oxygen decided to include bladder carcinoma in its clinical trials.

The First Trial

This trial was initiated at a time when the co-operating centres were already pursuing their own studies, so it was agreed that each centre should continue to employ its own radiotherapy regimen. The irradiation schedule in each centre was similar for cases in both arms of the trial but the patients were randomized to treatment in air or hyperbaric oxygen.

Four radiotherapy centres collaborated: Portsmouth, Mount Vernon, Glasgow and Oxford.

Method

Preliminary investigations of all patients included: chest X ray; full blood count; blood urea estimation; intravenous pyelography; examination under anaesthesia; bacterial culture of urine.

Patients were included in the trial if:

1. They had carcinoma of the bladder of any histological type and were considered suitable for an attempt to cure by radiotherapy using an external beam of high energy radiation.
2. The primary tumour had not extended to infiltrate the skin, the rectal wall or another segment of the intestine. Involvement of the vagina and uterus was allowed, provided there was no fistula.
3. Lymph node involvement was confined to the external iliac nodes. Patients were excluded if:

(a) there was impaired renal function, a blood urea greater than 100 mg-% (16.7 mmol/litre);
(b) they were unable to enter the chamber because
  (i) they were unable to lie flat for any reason
  (ii) they had a past history of fits or convulsions;
(c) they were unlikely or unable to co-operate in pressurization or in setting up for treatment inside the chamber;
(d) they resided abroad or co-existing disease made it unlikely that a course of treatment or follow-up could be completed;
(e) they had reached their 75th birthday.
(f) total cystectomy or urinary diversion had been performed.

If patients were accepted into the trial they were allocated to treatment in oxygen or in air by opening a sealed envelope containing instructions prepared by the Medical Research Council Statistical Research and Services Unit.

Radiotherapy techniques

Table I summarizes the protocols adopted by each of the centres. The patients who received treatment in oxygen were placed in a Vickers transparent chamber and the oxygen pressure was raised to three atmospheres absolute. Radiotherapy was delayed until 15 minutes after full pressure had been reached in order to allow time for the tumour to become saturated with oxygen. A correction was made for radiation absorbed in the chamber wall.

Results

From 1964 to 1971, 241 patients were entered into the trial and of these 236 patients were available for assessment. The actuarial survival rates are given in Table II.

TABLE I

PROTOCOLS ADOPTED BY THE COLLABORATING CENTRE

Centre	Period of entry to trial	Number of cases			Radiotherapy			Machine used
		T_1 & T_2	T_3 & T_4	Total	No. of fractions	Overall time (days)	Dose	
Portsmouth	May 64–Dec. 67	33	32	65	40	56	*6000 R	Cobalt 60
	Jan. 68–Dec. 71	34	23	57	6	18	†3600 rad	
Oxford	Dec. 68–Dec. 71	—	25	25	10	31	†4250 rad	Cobalt 60
Glasgow	Nov. 66–Feb. 70	18	9	27	24	34	‡6000 rad	4 MV
Mount Vernon	Apr. 66–May 71	21	20	41	30	42	6000 R	4 MV
		7	19	26	15	33	4725 R	

*Minimum tumour dose. †Maximum tissue dose. ‡Modal dose.

TABLE II

ACTUARIAL SURVIVAL RATES

	Total	Survival by years since entry to trial				
		1	2	3	4	5
Oxygen	118	75 (64%)	50 (42%)	42 (36%)	37 (31%)	33 (28%)
Air	118	76 (64%)	55 (47%)	44 (37%)	41 (35%)	36 (30%)

Probability of difference between curves arising by chance $P=0.72$.

TABLE III

ACTUARIAL SURVIVAL RATES ACCORDING TO HISTOLOGY

Histology	Treatment	Total patients	Percentage surviving by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Transitional	Oxygen	84	70	46	42	38	33	0.61
	Air	91	69	53	42	40	35	
Anaplastic	Oxygen	22	50	36	(27)	—	—	0.62
	Air	16	44	(19)	—	—	—	
Other	Oxygen	12	(42)	—	—	—	—	0.32
	Air	11	54	36	—	—	—	

At none of the individual centres, nor when the cases were gathered together, was any significant improvement in survival achieved by the use of hyperbaric oxygen, there being 28% survivors at five years among those treated in hyperbaric oxygen and 30% survivors among those treated in air ($P=0.88$).

An analysis of the results according to the different histological types of tumour (Table III) revealed no significant improvement of survival from either treatment regime.

In this trial data as to morbidity and local tumour control were not gathered centrally. In none of the reports from individual centres was any improvement in local control shown and no significant difference in morbidity was found (Dische, 1973; Wiernik and Perrins, 1974; Kirk *et al.*, 1976; Cade and McEwen, 1978). This information has been collected in all subsequent trials including the second bladder trial.

THE SECOND TRIAL

By 1971, it appeared that the best results for treatment given in hyperbaric oxygen followed the use of a relatively few (up to ten) fractions. This was consistent with the radiobiological data then being reported. Withers and Scott (1964) showed that the oxygen enhancement ratio (OER) on normal mouse skin is dependent on radiation dose. Révész and Littbrand (1974) concluded from studies on irradiated Chinese hamster cells that the sensitivity of anoxic and oxic populations will vary with the radiation dose delivered and that the OER of a 400 rad fraction is approximately 2.07, whereas it is negligible for fractions of less than 200 rad. Meanwhile, Rubin *et al.* (1969) had pointed out that the OER was more likely to be improved by a few fractions each with a large dose since the differential destruction between aerobic and anoxic cells occurs on the slope rather than the shoulder of a cell survival curve.

These considerations, amongst others, led to the working party initiating further studies to compare treatment given in a small number of fractions in hyperbaric oxygen with a treatment schedule suitable for conventional radiotherapy in air where a greater number of fractions are usually employed. Although 165 patients have so far been entered into this trial not enough time has elapsed yet for conclusions to be reached.

CONCLUSIONS

In this study which has involved the treatment of 241 patients, with an intake period of six to seven years and a follow-up period of over 13 years, oxygen has not given any improvement in survival. Local control and morbidity was not recorded centrally but with both no important differences between cases treated in oxygen and air were noted at each centre.

These results suggest either than hypoxic tumour cells do not significantly contribute to failure to cure in carcinoma of bladder, or that in this situation hyperbaric oxygen does not significantly contribute to the eradication of hypoxic tumour cells.

REFERENCES

Cade, I. S., and McEwen, J. B., 1978. Clinical trials of radiotherapy in hyperbaric oxygen at Portsmouth (1964–1976). *Clinical Radiology 29*, 333–338.

Dische, S., 1973. The hyperbaric oxygen chamber in the radiotherapy of carcinoma of the bladder. *British Journal of Radiology*, *45*, 13–17.

Kirk, J., Wingate, W. H., and Watson, E. R., 1976. High-dose effects in the treatment of carcinoma of the bladder under air and hyperbaric oxygen conditions. *Clinical Radiology*, *27*, 137–144.

Révész, I., and Littbrand, B., 1974. Variation of the oxygen enhancement ratio at different X-ray dose levels and its possible significance. In *Advances in Radiation Research Biology and Medicine*, *3*, eds. J. F. Duplan and A. Chapiro, pp. 1215–1224 (Gordon and Breach, London).

Rubin, P., Poulter, C. A., and Quick, R. S., 1969. Changing perspectives in oxygen breathing and radiation therapy. *American Journal of Roentgenology*, *105*, 665–681.

Wiernik, G., and Perrins, D. J. D., 1974. Hyperbaric oxygen and radiotherapy in advanced carcinoma of the cervix and bladder. In *Fifth International Hyperbaric Congress Proceedings*, *II*, pp. 820–829 (Vancouver, B.C.).

Withers, H. R., and Scott, O. C. A., 1964. British Empire Cancer Campaign Report, p. 233.

1978, *British Journal of Radiology*, *51*, 879–887 NOVEMBER 1978

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix

By E. R. Watson, M.B., F.R.C.R., and K. E. Halnan, F.R.C.P., F.R.C.R., F.R.S.E.,
Glasgow Institute of Radiotherapeutics, Western Infirmary, Glasgow G11 6NT

S. Dische, M.D., F.R.C.R., and M. I. Saunders, M.B., F.R.C.R.,
Marie Curie Reserach Wing for Oncology, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

I. S. Cade, M.S., F.R.C.S., F.R.C.R., and J. B. McEwen, M.B., F.R.C.R.,
Department of Radiotherapy and Oncology, St. Mary's General Hospital, Portsmouth PO3 6AD

G. Wiernik, M.D., F.R.C.R., and D. J. D. Perrins, M.D., F.R.C.S.,
Research Institute, The Churchill Hospital, Headington, Oxford OX3 7LJ

and I. Sutherland, M.A., D.Phil.
MRC Statistical Research and Services Unit, University College Hospital Medical School, 115 Gower Street, London WC1E 6AS

(*Received April, 1978*)

ABSTRACT

In a randomized controlled clinical trial of hyperbaric oxygen in the radiotherapy of advanced carcinoma of the uterine cervix a total of 320 cases were contributed by four radiotherapy centres in the United Kingdom. The use of hyperbaric oxygen resulted in improved local control and survival. The benefit was greatest in patients under the age of 55 who presented with stage III disease. There was a slight increase in radiation morbidity but it seemed that the benefit of hyperbaric oxygen outweighed this increase in morbidity and that there was a true improvement in the therapeutic ratio.

The Medical Research Council's working party on radiotherapy and hyperbaric oxygen included carcinoma of cervix as one of their sites for prospective randomized clinical trials. The tumour seemed suitable because the more advanced stages are treated

TABLE I

PLAN OF TREATMENT EMPLOYED AT PARTICIPATING CENTRES

		Radiotherapy				
Centre	Period of entry to trial	No. of fractions	Overall time (days)	Dose	Machine used	Further routine treatment
Portsmouth	Jan. 68–Oct. 72	6 (first 20 cases) 7	18 22	3600 rad (max) 3500 rad (max)	Cobalt 60	None
Oxford	Dec. 68–Dec. 71	10	31	4250 rad (max)	Cobalt 60	Surgery performed in 5 cases. Radium applied in remainder.
Glasgow	Aug. 66–Feb. 73	20	28	4500 rad (modal) (first 10 cases only) 4250 rad (modal)	4MV Linear Accelerator	All cases single radium insertion—3500 rad at point 'A'
Mount Vernon	Feb. 66–Dec. 71	27	38	5500 R (min)	4MV linear accelerator	All cases single radium insertion—2000 R at point 'A'

MRC HYPERBARIC OXYGEN TRIALS
PROGRESS REPORT
(at six monthly intervals)

Hospital reference number ☐

PATIENT'S NAME...

ALLOCATION LETTER (IF ANY) AND NUMBER ☐☐

CENTRE ....

TREATMENT ALLOCATED: O orA ☐

NO. OF FRACTIONS ☐

DATE EXAMINATION DUE ....

INTERVAL SINCE START OF TREATMENT ☐ months

DATE PATIENT EXAMINED.................................
(Preferably within one month either way of due date)
If patient has died, enter findings at PM or, if no PM, those at last previous examination

RESIDUAL TUMOUR OR RECURRENCE
(in treated volume)
Code: (enter code no.)

0. No Tumour
1. Possible tumour
2. Clinically definite
3. Histologically proved

If 2 or 3, date first diagnosed:
☐☐☐

METASTATIC TUMOUR OR TUMOUR SITE: (enter code no.)
OUTSIDE TREATED VOLUME
Code:

0. No tumour
1. Possible tumour
2. Clinically definite
3. Histologically proved

If 2 or 3, date first diagnosed:
☐☐☐

LYMPH NODES ☐
LUNG ☐
LIVER ☐
BONE ☐
BRAIN ☐
OTHER (specify) ☐

TREATMENT SINCE LAST PROGRESS REPORT (on...............................)
(Tick where applicable)

Surgery ☐
Radiotherapy ☐
Chemotherapy ☐

PURPOSE: (Tick where applicable)

For disease in treated volume ☐
For disease outside treated volume ☐
Surgery for necrosis ☐
Other (specify)............................... ☐

POST RADIATION DAMAGE
(at time of examination)

Code:

0. None
1. Slight
2. Moderate
3. Severe (causing disability)

SITE (Enter code number)

HEAD & NECK
Cartilage ☐
Bone ☐
Persistent oedema ☐
Skin ☐

LUNG ☐
BOWEL ☐
BLADDER ☐
CERVIX ☐
VAGINA ☐

OTHER (Specify) ....

DEATH

PM EXAMINATION 1. Yes 2. No ☐

DATE OF DEATH.......................

CAUSE OF DEATH: (Enter code no.)

Code:

0. Not present
1. Present but not contributing to death
2. Contributing to death but not primary cause
3. Primary cause of death

Treated carcinoma (primary and/or metastases) ☐
Post-radiation damage (including radiation-induced neoplasm) ☐
Complications of surgery or chemotherapy for carcinoma ☐
Co-incidental disease (including other neoplasms) ☐

Date form completed..

Signed....................................

Fig. 1. Follow-up *pro forma*.

essentially by radiotherapy and failure to control the disease locally is a major problem.

The working party agreed upon the following criteria for admitting patients to the trial:

(1) age not greater than 75 years;
(2) locally advanced disease confined to the pelvis (stages III and IVa, Stockholm);
(3) diagnosis proven histologically;
(4) the patient able to lie flat and be otherwise fit for treatment in the hyperbaric oxygen chamber;
(5) no previous treatment with radium.

TABLE II

NO. OF PATIENTS ADMITTED AT EACH CENTRE, ACCORDING TO STAGE

Centre	Treatment series	No. of patients	Stage II	Stage III	Stage IV
Portsmouth	Oxygen Air	19 18	0 0	19 18	0 0
Oxford	Oxygen Air	17 17	0 0	11 12	6 5
Glasgow	Oxygen Air	80 82	0 0	58 69	22 13
Mount Vernon	Oxygen Air	45 42	12 11	31 25	2 6

TABLE III

DISTRIBUTION OF HISTOLOGICAL TYPES

	Squamous	Adeno	Anaplastic
Oxygen	150	7	4
Air	151	7	1
Total	301	14	5

Each collaborating centre was permitted to employ its own regime of radiotherapy as regards dose, number of fractions and overall time of treatment. However, similar radiotherapy was to be given to all patients whether they were randomized to air or to hyperbaric oxygen. It was recognized that the addition of a radium application at the end of the course of external beam therapy would complicate the interpretation of the result because it is not possible to enclose a patient in a hyperbaric oxygen chamber for the period when radium is in place. The working party decided, however, that centres should be permitted to employ a radium application if they regarded it as an essential part of management.

The working party originally planned to assess the results of the trial by the survival time and also by post-mortem determination of the presence or absence of active tumour. As experience was gained, however, greater stress was laid upon the continued follow-up of the patients after treatment so as to determine the presence or absence of tumour within the treatment volume, the incidence of local morbidity and the appearance of distant metastases.

Cases were contributed to the study by four radiotherapy centres: Portsmouth, Oxford, Glasgow and Mount Vernon. Details of management in each centre are shown in Table I. A small number of patients with advanced stage IIb disease (tumour extending more than halfway to pelvic wall) were included by Mount Vernon.

TABLE IV

ACTUARIAL SURVIVAL RATES ACCORDING TO CENTRE (ALL PATIENTS)

Centre	Treatment series	Total patients	Percentages surviving by years since entry to trial 1	2	3	4	5	Probability of difference between curves due to chance
Portsmouth	Oxygen Air	19 18	74 67	47 28	42 17	42 17	42 8	0.11
Oxford	Oxygen Air	17 17	53 65	41 41	35 24	35 12	35 0	0.52
Glasgow	Oxygen Air	80 82	71 66	53 49	45 36	39 34	31 28	0.24
Mount Vernon	Oxygen Air	45 42	82 69	60 50	47 41	40 38	30 38	0.91
All patients	Oxygen Air	161 159	73 67	53 46	44 34	40 31	33 27	0.08

TABLE V

ACTUARIAL SURVIVAL RATES ACCORDING TO STAGE

Stage	Treatment series	Total patients	Percentages surviving by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
IIB	Oxygen	12	92	67	58	42	42	0.034
	Air	11	91	73	73	73	73	
III	Oxygen	119	77	57	49	45	37	0.012
	Air	124	70	49	34	30	25	
IV	Oxygen	30	47	30	20	16	16	0.76
	Air	24	38	17	17	17	17	
All patients	Oxygen	161	73	53	44	40	33	0.08
	Air	159	67	46	34	31	27	

TABLE VI

ACTUARIAL SURVIVAL RATES ACCORDING TO CENTRE (STAGE III PATIENTS ONLY)

Centre	Treatment series	Total patients	Percentages surviving by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Portsmouth	Oxygen	19	74	47	42	42	42	0.11
	Air	18	67	28	17	17	8	
Oxford	Oxygen	11	73	55	46	46		0.26
	Air	12	75	50	25	8		
Glasgow	Oxygen	58	78	60	55	50	38	0.10
	Air	69	73	55	40	37	31	
Mount Vernon	Oxygen	31	81	58	42	39	28	0.66
	Air	25	64	48	32	28	28	
All patients	Oxygen	119	77	57	49	45	37	0.009*
	Air	124	70	49	34	30	25	

*After adjusting for differences in the distribution of oxygen and air patients between the centres (cf. Table V which gives the unadjusted figure of 0.012).

The procedure for randomization was identical in all centres. After admission to the trial, selection of treatment in hyperbaric oxygen or air was determined by opening the next in a numbered batch of envelopes supplied by the Medical Research Council's Statistical Research and Services Unit. The first patient was randomized in February 1966 and the last in February 1973. The *pro formas* designed for the trial underwent development while it was proceeding. The follow-up *pro forma* now in use for continued follow-up of these patients and for the other hyperbaric oxygen trials is shown in Fig. 1.

At the time entry to the study was terminated in February 1973, a total of 320 patients had been included (Table II). A second clinical trial was underway at this time in which six treatments in hyperbaric oxygen were being compared with 27 in air.

RESULTS AND DISCUSSION

Squamous cell carcinoma accounts for 301 of the 320 cases, the remainder being classified as adenocarcinoma or anaplastic (Table III). The overall survival of the patients is shown in Table IV. In each centre the margin of benefit lies with hyperbaric oxygen; however, in none does it approach statistical significance. When all the cases are added together the probability that oxygen confers an advantage reaches close to a significant level.

In Table V the relationship of survival to stage is shown. In stage III, where the bulk of the cases are

TABLE VII

ACTUARIAL SURVIVAL RATES ACCORDING TO AGE (STAGE III PATIENTS ONLY)

Age	Treatment series	Total patients	Percentages surviving by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Under 35	Oxygen Air	3 2						0.84
35–44	Oxygen Air	17 10	82 50	77 40	65 40	59 40	53 40	0.12
45–54	Oxygen Air	42 52	88 77	74 58	67 40	64 35	48 28	0.008
55–64	Oxygen Air	38 38	66 68	37 47	34 34	29 29	26 23	0.90
65 and over	Oxygen Air	19 22	74 68	42 41	21 16	21 16	11 16	0.91
All stage III patients	Oxygen Air	119 124	77 70	57 49	49 34	45 30	37 25	0.038

TABLE VIII

ACTUARIAL METASTASIS-FREE RATES ACCORDING TO CENTRE

Centre	Treatment series	Total patients	Percentages free of metastases by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Portsmouth	Oxygen Air	19 18	83 94	71 86	71 86	62 58	53 58	0.81
Oxford	Oxygen Air	17 17	82 70	82 51	70 51	70 51	56 —	0.71
Glasgow	Oxygen Air	80 82	74 70	56 61	52 57	50 47	48 42	0.72
Mount Vernon	Oxygen Air	45 42	91 82	72 60	56 60	53 60	49 60	0.79
All patients	Oxygen Air	161 159	80 76	64 62	57 60	54 53	49 50	0.97

placed, there is a significant improvement in survival with hyperbaric oxygen ($P < 0.012$). Survival of patients treated in hyperbaric oxygen was 45% at four years compared with 30% for those treated in air. Although the margin is in favour of hyperbaric oxygen in the first two years after treatment of stage IVa disease, this disappears later and over the complete range of times there is no statistical difference between the curves of survival of these advanced cases. In stage IIb disease a difference develops in favour of air, but the number of cases is small and the difference is not significant. When the figures for stage III disease are considered at the individual centres (Table VI), benefit to hyperbaric oxygen is shown at each but significance is not reached at any one. This fully demonstrates the value of collaborative effort so as to gather adequate numbers of cases. When the stage III cases are divided by age at time of treatment (Table VII) it can be seen that the benefit of oxygen was obtained only in those below the age of 55.

The actuarial metastasis-free rates both for the patients treated in hyperbaric oxygen and in air show a close similarity (Table VIII) both for the individual centres and for all cases combined. The metastasis-free rates stage by stage also show no difference between oxygen and air; however, it is obvious that there is an increasing incidence of metastasis during follow-up with advancing stage of disease at the time of starting treatment (Table IX).

The actuarial local recurrence-free rates are shown according to centre in Table X. In each centre there is a considerable benefit to oxygen, reaching significance at Glasgow where the largest number of cases was treated. When all cases are considered together the benefit, ranging from 20 to 24% between two and five years after treatment, is significant at the <0.001 level. In Table XI we can see the recurrence-free rate related to stage. Once again benefit is shown in the stage III cases. None is seen in the small number of stage IIb cases. In stage IVa there is a margin in favour of oxygen from two to four years after treatment, but the difference is not significant.

The recurrence-free rates for each centre in the treatment of stage III patients are shown in Table XII. Benefit is shown with hyperbaric oxygen in each centre, this reaching significance at Glasgow and at Mount Vernon. An analysis of the stage III patients according to age (Table XIII) shows, as with survival, that the benefit occurs in the patients below the age of 55. Above the age of 55 the margin in favour of oxygen does not attain significance. The percentage of patients free of local disease in those under the age of 55 who were treated in hyperbaric oxygen is remarkably high.

Table XIV shows the post-radiation morbidity in these patients. This was recorded more frequently

TABLE IX

ACTUARIAL METASTASIS-FREE RATES ACCORDING TO STAGE (ALL PATIENTS)

Stage	Treatment series	Total patients	Percentages free of metastases by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
IIB	Oxygen Air	12 11	100 100	80 90	57 90	57 90	57 90	0.31
III	Oxygen Air	119 124	82 75	67 62	61 59	57 50	51 46	0.32
IV	Oxygen Air	30 24	66 63	44 43	39 43	39 43	39 43	0.58
All patients	Oxygen Air	161 159	80 76	64 62	57 60	54 53	49 50	0.97

TABLE X

ACTUARIAL LOCAL RECURRENCE-FREE RATES ACCORDING TO CENTRE

Centre	Treatment series	Total patients	Percentages free of local recurrence by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Portsmouth	Oxygen Air	19 18	65 46	58 18	58 18	58 18	58 18	0.07
Oxford	Oxygen Air	17 17	45 13	45 13	45 13	45 —	45 —	0.11
Glasgow	Oxygen Air	80 82	89 85	85 64	85 61	85 61	78 58	0.03
Mount Vernon	Oxygen Air	45 42	85 66	80 55	70 52	70 52	60 49	0.14
All patients	Oxygen Air	161 159	80 68	76 52	73 49	73 49	67 47	<0.001

among oxygen patients (26%) than among air patients (19%). Particularly in the bowel, morbidity was more often severe or moderate than in the air cases. This is also shown by Table XV which classifies the deaths by primary and contributory causes. Post-radiation damage was considered the primary cause or a contributory cause in nine of the 108 deaths in hyperbaric oxygen patients but only in four of the 123 deaths among those treated in air.

As is shown in Table I there were considerable differences in technique between the centres. A small number of fractions (six to ten) was employed at Portsmouth and Oxford with a larger number (20 or 27) at Glasgow and Mount Vernon. At Portsmouth radium was not employed after external beam therapy unlike the practice at the other three centres. At Oxford five patients underwent hysterectomy following radiotherapy but this was not performed elsewhere.

A comparison of the results shows that local recurrence-free rates tended to be lower at Portsmouth and Oxford especially in the cases treated in air, when compared with the results at Glasgow and Mount Vernon. Although this also applied when stage II cases only are considered, a difference in the spectrum of the cases seen at the different centres cannot be excluded and we must be cautious in drawing any conclusion.

Benefit from hyperbaric oxygen would be expected to show most significantly when radium was not employed and when all the radiotherapy was given either in hyperbaric oxygen or in air. This may be relevant to the large difference in the results of treatment in hyperbaric oxygen and air at Portsmouth.

TABLE XI

ACTUARIAL LOCAL RECURRENCE-FREE RATES ACCORDING TO STAGE (ALL PATIENTS)

Stage	Treatment series	Total patients	Percentages surviving by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
IIB	Oxygen Air	12 11	91 73	81 73	61 64	61 64	61 64	0.83
III	Oxygen Air	119 124	82 67	77 50	76 47	76 47	71 44	<0.001
IV	Oxygen Air	30 24	71 77	71 53	71 53	71 53	48 53	0.81
All patients	Oxygen Air	161 159	80 68	76 52	73 49	73 49	67 47	<0.001

TABLE XII

ACTUARIAL LOCAL RECURRENCE-FREE RATES ACCORDING TO CENTRE (STAGE III PATIENTS ONLY)

Centre	Treatment series	Total patients	Percentages local recurrence-free by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Portsmouth	Oxygen Air	19 18	65 46	58 18	58 18	58 18	58 18	0.07
Oxford	Oxygen Air	11 12	46 13	46 13	46 13	46	46	0.15
Glasgow	Oxygen Air	58 69	92 84	87 64	87 60	87 60	80 57	0.011
Mount Vernon	Oxygen Air	31 25	86 60	81 46	76 46	76 46	69 40	0.037
All stage III patients	Oxygen Air	119 124	82 67	77 50	76 47	76 47	71 44	<0.001

TABLE XIII

ACTUARIAL LOCAL RECURRENCE-FREE RATES ACCORDING TO AGE (STAGE III PATIENTS ONLY)

Age	Treatment series	Total patients	Percentages local recurrence-free by years since entry to trial					Probability of difference between curves due to chance
			1	2	3	4	5	
Under 35	Oxygen	3						
	Air	2						
35–44	Oxygen	17	88	81	81	81	73	0.12
	Air	10	50	50	50	50	38	
45–54	Oxygen	42	90	90	90	90	85	0.001
	Air	52	70	54	51	51	51	
55–64	Oxygen	38	69	65	65	65	57	0.50
	Air	38	71	50	47	47	42	
65 and over	Oxygen	19	76	59	49	49	49	0.53
	Air	22	63	40	40	40	40	
All patients	Oxygen	119	82	77	76	76	71	<0.001
	Air	124	67	50	47	47	44	

TABLE XIV

POST-RADIATION MORBIDITY

Treatment series	Severity	No. of patients	Morbidity in these patients, by site				
			Bowel	Bladder	Cervix	Vagina	Other
Oxygen (161 pts)	Severe	20	13	8	3	7	5
	Moderate	13	5	2	2	6	3
	Slight	9	5	4	1	2	0
Air (159 pts)	Severe	6	2	3	1	4	1
	Moderate	8	7	1	1	1	1
	Slight	16	8	4	2	3	2

TABLE XV

DEATHS BY CAUSE

Treatment series	Total deaths	Importance of cause	Cause			
			Treated carcinoma	Post-radiation damage	Complications of other treatment	Coincidental disease
Oxygen	108*	Primary cause of death†	87	6	1	8
		Contributory, but not primary	5	3	2	4
		Present, but not contributory	0	1	0	0
Air	123**	Primary cause of death	107	3	0	9
		Contributory, but not primary	5	1	0	4
		Present, but not contributory	4	4	1	1

*Cause not stated in three patients.
**Cause not stated in one patient.
†Primary cause not stated in three more patients.

There is a suggestion from the data that although hyperbaric oxygen gave benefit with all the fractionations tested it was particularly beneficial when six to ten fractions were employed. Recognizing the lower than average survival and recurrence-free rates seen in those patients treated with six to ten fractions in air it must be added that such fractionation may, in air, be a poor treatment for advanced carcinoma of the cervix compared with 20 or more fractions also given in air. It is, however, noteworthy that hyperbaric oxygen significantly improved the recurrence-free rates at the centres using 20 or more fractions, at Glasgow for all stages (Table X) and both at Glasgow and Mount Vernon for stage III only (Table XII).

CONCLUSIONS

In this randomized controlled clinical trial of treatment of carcinoma of cervix a valuable improvement in local tumour control and in survival has been achieved with hyperbaric oxygen. This is shown most particularly in patients with stage III disease who are under the age of 55. Older patients, and particularly those with Stage IVa disease, show little if any benefit.

This improvement in tumour control has been at the expense of some increase in morbidity. In view of the overall improvement in survival in the stage III cases, it would seem that the improvement in cure of the primary tumour outweighs the increase in morbidity and that a real improvement in the therapeutic ratio has been achieved with the use of the hyperbaric oxygen chamber in carcinoma of the uterine cervix.

ACKNOWLEDGMENTS

The authors wish to thank their colleagues in gynaecology, pathology and radiotherapy who co-operated in the work. At Glasgow the contribution of Dr. S. Morris in the early stages of the trial was particularly appreciated. They also wish to thank the junior medical staff, radiographers, nurses and secretaries who all made their essential contributions, and Mrs E. Davies for the preparation of the manuscript. The support of the Medical Research Council at all four centres is gratefully acknowledged.

1979, *British Journal of Radiology*, *51*, 888–894

Hyperbaric oxygen: the Medical Research Council trials and their clinical significance

By S. Dische, M.D., F.R.C.R.

Marie Curie Research Wing for Oncology, Regional Radiotherapy Centre, Mount Vernon Hospital, Northwood Middlesex HA6 2RN

(*Received April, 1978*)

ABSTRACT

The clinical trials of the use of hyperbaric oxygen in radiotherapy conducted by the Medical Research Council's working party have shown that local cure and survival can be improved in head and neck and cervical cancer. Evidence for benefit has been presented in carcinoma of bronchus, but none has so far been found in carcinoma of the bladder.

Although hyperbaric oxygen has produced increased effect upon normal tissues as well as upon tumour, a real improvement in therapeutic ratio appears to be present.

The future use of hyperbaric oxygen in radiotherapy will depend upon a comparison of effectiveness with other methods now being tested to improve radiotherapy.

The trials have yielded much fundamental and clinical data of general relevance in the radiotherapy of malignant disease.

At the Annual Congress of The British Institute of Radiology in April, 1977 papers were presented describing the results obtained in the Medical Research Council's trials of the use of hyperbaric oxygen in radiotherapy of tumours at four sites—the head and neck, uterine cervix, bladder and bronchus. Publication of the results obtained in the head and neck region (Henk *et al.*, 1977; Henk and Smith, 1977) and in the bronchus (Cade and McEwen, 1978) has now been followed by the results in the bladder and uterine cervix (Cade *et al.*, 1978; Watson *et al.*, 1978). A general report of the work of the working party has also been published (Medical Research Council, 1978).

THE SITES OF TUMOUR, THE RESULTS OBTAINED AND CONCLUSIONS TO BE DRAWN

There have been many reports of the value of hyperbaric oxygen in clinical radiotherapy. Most have been concerned with a series of cases of one or of many different types of tumour treated in the oxygen chamber and in which a careful comparison has been made with previous or currently treated cases managed conventionally. These works have been valuable contributions to the development of the technique but cannot be of help in determining the definitive place for hyperbaric oxygen in radiotherapy. For this purpose we can only consider prospective randomized controlled trials.

(*a*) *Head and neck cancer*

The first Cardiff trial, in head and neck cancer, was carried out in association with the Medical Research Council working party (Henk *et al.*, 1977). In this trial a dose between 3500 and 4600 rad was given, depending on the field size, in ten fractions over 22 days in hyperbaric oxygen or in air. A total of 295 patients were admitted and a significantly higher local tumour control rate was obtained with hyperbaric oxygen, 53% compared with 30% with air ($P < 0.001$). This resulted in a reduced necessity for salvage surgery but not in a significant improvement in survival. There was significantly higher morbidity when the larynx was included in the treatment volume.

In the second trial, begun in 1971, the identical dose and fractionation was retained for hyperbaric oxygen except where the larynx was in the field of treatment when the dose was reduced by 10% (Henk and Smith, 1977). The control group received a conventional daily fractionation scheme in air. By June, 1976, 104 patients had been entered at Cardiff where the control group was treated in air using 30 fractions over a period of six weeks with tumour doses up to 6400 rad. At Leeds 23 patients were included in the trial, the air cases being treated with the daily fractionation regime normally used by the referring consultant (Berry, 1978). Preliminary results assessed from one to four years after treatment indicate not only a significant improvement in local control ($P < 0.001$) but also in survival ($P < 0.01$); figures for local control with hyperbaric oxygen show an improvement in local control compared with treatment in air by 21–28% (MRC, 1978). Despite the reduction in dose for the larynx cases, treatment in hyperbaric oxygen remained superior for these cases. No excess morbidity has been seen in this second trial.

The trials indicate that hyperbaric oxygen can improve the results of the radiotherapy of head and neck cancer. Although there have been many contributions on this subject, only three prospective randomized controlled trials in head and neck cancer have been reported apart from the Medical Research Council studies. Van den Brenk (1968) showed a significant increase in local clearance of tumour after radiotherapy with hyperbaric oxygen as compared with air in a series of 29 cases. Follow-up of these cases has not been reported. Chang *et al.*, (1973) included 51 patients in a trial of hyperbaric oxygen in oropharyngeal cancer. Six fractions were employed in oxygen, seven or 30 in air. The margin of benefit lay with hyperbaric oxygen both for local control and survival, but these did not achieve statistically significant levels. Shigematsu *et al.*, (1973) obtained a similar result when they randomized 42 cases of antral carcinoma to either 4–5000 rad in eight to ten fractions in hyperbaric oxygen or to 6–7000 rad in 12 to 14 fractions in air; in both groups they used twice-weekly treatments and 500 rad for individual treatments. The margin of benefit both for local control and survival was in favour of hyperbaric oxygen, but did not achieve statistical significance. It must be pointed out that in both trials the limited number of cases would have prevented even the substantial margin shown at Cardiff from reaching significance. We can conclude that all the evidence available is in keeping with the view that hyperbaric oxygen is of benefit in the radiotherapy of head and neck cancer.

(*b*) *Carcinoma of the bladder*

In the first Medical Research Council trial in carcinoma of bladder no benefit was shown with hyperbaric oxygen (Cade *et al.*, 1978). An examination of the results in the 236 cases which were assessed showed no margin favouring oxygen. Morbidity was not recorded centrally in this early trial. Van den Brenk (1968) randomized 16 patients to treatment, either in oxygen using six fractions and a total dose of 3000 rad or air using six fractions and 3300 rad. There was a considerable margin of benefit in terms of local clearance but this was not of statistical significance and long term follow-up was not reported. Plenk (1972) randomized 40 patients to either 4800 rad in 12 fractions in hyperbaric oxygen or to 6000 rad in 24–30 fractions in air. Survival at two years was 37% for oxygen and 19% for air. The difference in the survival curves was significant at the $P = 0.05$ level. There is no report of the morbidity although this is important, particularly in a trial where different dose and fractionation regimes were employed in oxygen compared with air.

The first Medical Research Council trials were performed mainly, although not entirely, using a large number of small fractions, rather more than in the work of Van den Brenk and of Plenk. In the second trial six fractions are being employed in hyperbaric oxygen and this is being compared with 14 in air. Entry to the trial has been concluded, follow-up is continuing and an assessment will soon be made.

We may conclude that, so far, the bulk of evidence suggests that hyperbaric oxygen does not improve the result of radiotherapy in cancer of the bladder.

(*c*) *Carcinoma of the bronchus*

In a series of trials in carcinoma of bronchus performed at Portsmouth in collaboration with the Medical Research Council's working party in hyperbaric oxygen a total of 280 patients were randomized between January, 1964 and October, 1976 (Cade and McEwen, 1978). Using conventional small daily fractions, 40 fractions over eight weeks to a dose of 6000 R and 30 fractions over six weeks to 4500 R, the trial did not show any improvement in survival using hyperbaric oxygen. When six fractions each of 600 rad maximum tissue dose in 18 days were employed, however, hyperbaric oxygen led to improved survival. This improvement was most clearly shown in the 123 patients with squamous cell carcinoma. Survival at two years after treatment in hyperbaric oxygen was 24·6% compared with 12·4% in air and at four years 15·9% compared with 2·5% in air. The trial is to be continued but with an intensified investigation prior to treatment, employing stricter criteria for entry to exclude patients with occult metastasis. Cade and McEwen suggest that a group of patients may emerge where the results of radiotherapy when combined with hyperbaric oxygen may equal that of surgery. The controlled trials at Portsmouth using hyperbaric oxygen in carcinoma of the bronchus cannot be matched by any other work.

(*d*) *Carcinoma of the cervix*

Here there is a complex situation. Benefit has been shown in the Medical Research Council study which included four centres in the United Kingdom (Watson *et al.*, 1978). Including all 320 cases randomized, there was an increase in local tumour control by 20 to 24% at two to five years after treatment and this was highly significant ($P < 0.001$). The greatest benefit was seen in stage III where there was also a significant improvement in survival. This benefit in tumour control was achieved with some increase in morbidity. A remarkable finding in the United Kingdom trials was that the main benefit seems to be achieved in patients below the age of 55. As yet no significant improvement has been shown at Cape Town and results in sub-groups given different regimes of fractionation show a rather different pattern from that which has emerged in the United Kingdom trials.

At Leeds an analysis of 75 cases in a trial in stage IIb and III disease has shown no benefit to oxygen and no increase in morbidity (Ward, *et al.*, 1978). The external beam therapy was given in ten fractions in both oxygen and air. The technique included a large contribution from three intra-cavitary applications of radiocobalt using the cathetron and this may have weighed the trial against showing benefit from a modification in the external beam therapy.

An extensive trial of hyperbaric oxygen in carcinoma of the cervix has been performed at Houston (Fletcher *et al.*, 1977). A total of 233 patients in stages IIb, III and IVa was randomized from September 1968 to March 1974. A complex protocol was employed featuring in some cases exploratory laparotomy and lymphadenectomy and in others extension of radiotherapy to the para-aortic nodes. No significant benefit and also no significant increase in morbidity was reported; however, the margin of local control in the pelvis was in favour of hyperbaric oxygen—20 of 109 (18%) failing in oxygen compared with 29 of 124 (23·5%) in air; further, the margin of morbidity lay with hyperbaric oxygen: 26 cases compared with 15.

Smaller series have been reported by Glassburn *et al.*, (1974) and Glassburn *et al.* (1977) containing 40 and 33 cases, where there has been no benefit in terms of survival but increased morbidity was noted with hyperbaric oxygen. With such small numbers no firm conclusions can be drawn.

When considering the overall results when the hyperbaric oxygen chamber is used in radiotherapy of carcinoma of the cervix we cannot draw any simple conclusions.

(*e*) *Discussion*

When we look at the results of the trials we need to find some explanation for the differences encountered. Why should hyperbaric oxygen contribute in head and neck tumours but not in bladder tumours? We know that hypoxia is a problem in nearly all the solid tumours which have been studied in animals, although the percentage of hypoxic cells and the biological characteristics of these tumours vary from one to another. In man we have little data to guide us, but it seems unlikely that human tumours are greatly different. Hypoxia is likely to be a problem in all human cancer, including bladder cancer; perhaps it is such a severe problem in the bladder that hyperbaric oxygen is not able to influence it sufficiently to improve the results. We must, of course, recognize that causes other than hypoxia exist for radiation failure, and if other factors dominate then this might account for the findings in carcinoma of bladder.

A possible explanation for the inconsistencies in the results of different trials of hyperbaric oxygen in carcinoma of the cervix may lie in the existence of differing types of tumour at this one site. It is conceivable that biological differences may exist between such tumour types so that hyperbaric oxygen may be beneficial in some patients but not in others.

Aitken-Swan and Baird (1966) suggested that there are two types of carcinoma of cervix, one which appears after an *in situ* phase and usually in middle-life, and one which appears *de novo* often in older patients. When we compare the United Kingdom series with those in Cape Town and Houston we find that the pattern of development of metastasis is rather different. If we look at the actuarial metastasis-free rate we find that at four years the figures at Glasgow and Mount Vernon are identical at 52% whereas at Cape Town it is 77%. This much lower metastasis rate at Cape Town is very similar to that reported from Houston (Carlson *et al.*, 1967). This difference in the incidence of distant metastasis may be associated with other biological differences in the primary tumours. Considerable differences in the distribution of tumours among the anatomical sites are seen when comparing racial groups; however, we assume a biological similarity regardless of racial origin when a tumour originates in a single site such as the cervix. This assumption may not be true. A dissimilarity may be relevant to the hyperbaric oxygen trials because the racial composition of the patients included in Cape Town and Houston was different to that in the United Kingdom.

If this explanation for the discrepancies in the results is substantiated it may have considerable significance in oncology. We will need to make careful studies to determine the biological characteristics of tumours under treatment and to try and correlate them with the radiation effects achieved. In this way we may be able to determine the optimum conditions for total dose, fractionation, overall time and means of sensitization or adjuvant therapy in each individual case so as to produce the best result.

HYPERBARIC OXYGEN AND THE THERAPEUTIC RATIO

The results of the Medical Research Council trials leave no doubt that hyperbaric oxygen applied in the radiotherapy of certain malignancies does increase the response observed in the tumour. We have, however, also seen evidence for an increased effect upon normal tissue. It is right, therefore, to question whether all could have been achieved by a simple elevation of radiation dose.

One approach towards an answer to this question is to determine either the amount by which the dose given under normal conditions in air must be raised so as to give the increment of normal tissue damage found with hyperbaric oxygen, or else the reduction of dose in oxygen so that the morbidity associated with normal treatment in air is produced. In the second Cardiff trial the dose given in hyperbaric oxygen was reduced by 10% when the larynx was included in the field of treatment (Henk and Smith, 1977). This reduction is a large one and we should not be misled into thinking that this is a generally applicable figure. The larynx, as Dr. Churchill-Davidson in his pioneer work has shown, is a special site with an unusually high percentage of *normal* cells which are hypoxic (Churchill-Davidson *et al.*, 1966). Although morbidity was generally slightly greater in hyperbaric oxygen in the first Cardiff trial, no significant increase in effect upon other normal tissues was detectable and in the second trial no reduction in dose has been made when the larynx was not included in the treatment field.

Different normal tissues have different thresholds of radiation dose before damage becomes apparent, and the steepness in the rise in incidence of morbidity with dose from that point also varies from tissue to tissue. For example, we may attempt to give a second course of treatment where the tumour is in certain sites in the head and neck region, but not when it is intimately related to intestine. The intestine is, in fact, a fairly sensitive normal structure and certainly when we irradiate the bladder or cervix in the treatment of carcinoma this is the main site of morbidity. There was a high incidence of morbidity in patients with carcinoma of cervix given radiotherapy at Cape Town in ten fractions over five weeks to a dose of 4500 rad, given either in oxygen or in air, and it has been shown how much this is reduced by bringing the total dose down to 4000 rad (Bennett *et al.*, 1977).

We at Mount Vernon, in co-operation with Cape Town, also attempted to give the dose of 4500 rad in ten fractions, but abandoned the attempt because of morbidity. Of the six patients in whom we attempted to achieve this high dose, three suffered severe morbidity and two of these patients died as a result of it. The other three suffered a moderate level of morbidity. In the next eight patients where the dose was reduced to 4000 rad, as in South Africa, we had one case of severe morbidity, one slight and six who experienced none whatsoever.

We can see that an increment in dose of about 12% leads, in this sensitive situation, to a very great increase in morbidity. In another experience we were able to observe in the clinic an increase in immediate reactions when patients were inadvertently given only a 3% increase in dose when irradiated for pelvic tumours. The increased bowel morbidity with hyperbaric oxygen reported in the Medical Research Council cervix trial was only detected by a long-term analysis of late morbidity and this was not apparent in the departments concerned with the patients on a day-to-day basis. It seems likely, therefore, from this evidence that the increment of morbidity in hyperbaric oxygen is, in terms of the increment of dose given under normal conditions in air, not likely to exceed 3%.

We can examine the published data to estimate the benefit in tumour control to be expected from an elevation in dose of 3% (Shukovsky, 1970, 1974; Moench and Philips, 1972; Morrison, 1975; Stewart and Jackson, 1975). A range of increment in control between three and 14% is obtained according to the author and the level chosen on their published curves (Fig. 1). All these values fall considerably short of the benefit seen with hyperbaric oxygen in both the head and neck and the cervix trials where local control was improved by figures ranging from 21 to 41% according to site and time interval after treatment.

THE FUTURE OF HYPERBARIC OXYGEN IN RADIOTHERAPY

As a method introduced to improve radiotherapy, hyperbaric oxygen is the only one which has been found to be effective in clinical trials where the conditions of test may be regarded as fully acceptable. During the past decade, while the hyperbaric oxygen trials were being performed, other methods for improving the local results of radiotherapy have been introduced. These include the addition of cytotoxic chemotherapy, modifications in the fractionation as to total number and time relationships, the use of heavy particles such as neutrons and pions, and the use of chemical agents as hypoxic cell sensitizers. The benefits which have been shown in the hyperbaric oxygen trials will now have to be measured against these more recently introduced techniques. In the meantime those centres presently equipped with hyperbaric chambers will use them for those tumours where benefit has been shown. A number of trials with hyperbaric oxygen are not yet complete and follow-up of all cases included in the earlier studies must continue. An increase in the number of centres with hyperbaric chambers will

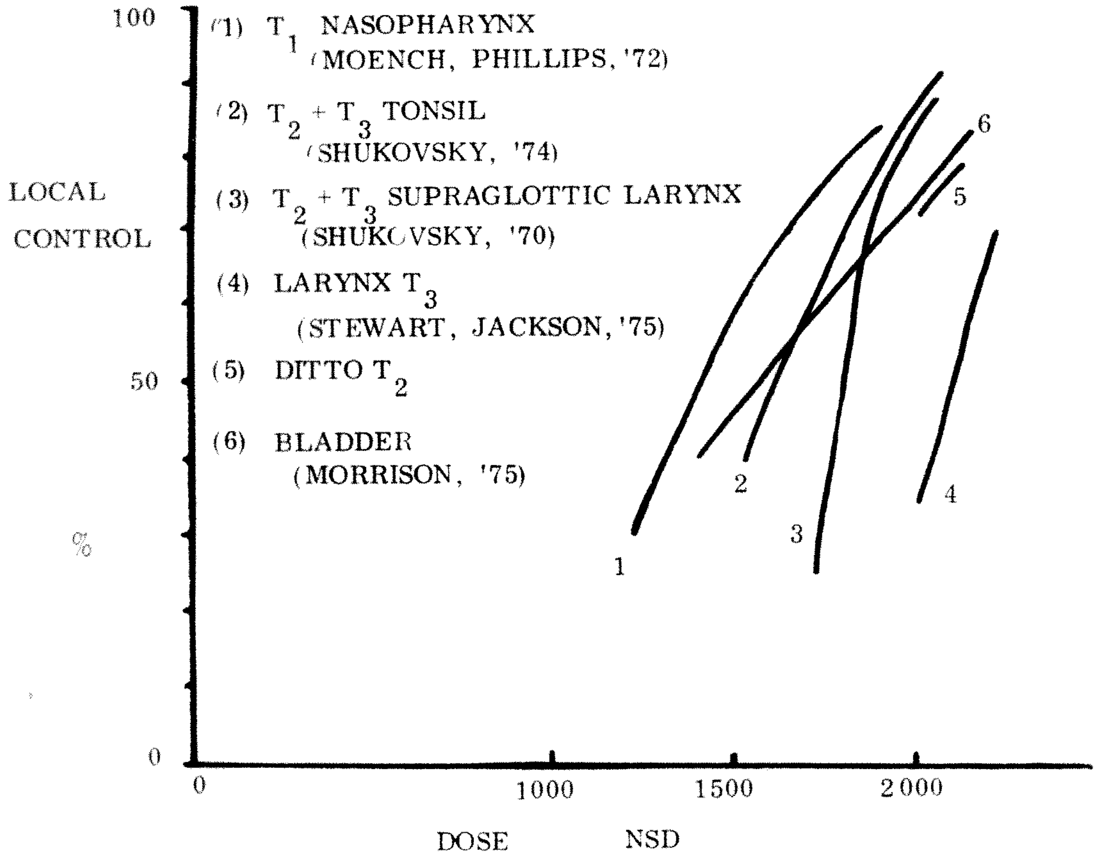


FIG. 1.

The relationship between local control and dose as reported in five publications. See text for significance in interpretation of hyperbaric oxygen trials. (This modification of an unpublished figure prepared by Professor J. F. Fowler is presented here with his kind permission.)

only follow if the technique is shown to be superior to the other methods now under trial.

THE VALUE OF THE HYPERBARIC OXYGEN TRIALS

Hyperbaric oxygen has been used in radiotherapy for nearly 25 years. Enthusiasm for a new method has faded and much scepticism has been voiced, some of it based on emotional reaction to the presence of one of these monsters in the radiotherapy treatment room. The clinical trials which have kept the method going have now yielded a vast amount of fundamental and clinical information in addition to determining the benefit in some tumour sites and the lack of advantage in others.

Much radiobiological data has been gathered which will have an influence throughout the whole field of radiotherapy. We can certainly conclude that at a daily dose increment as small as 200 rad hyperbaric oxygen does increase the effects upon both tumour and normal tissues. This is in opposition to what might be expected from an over simplified radiobiological model. The exploration of multiple doses of this order with experimental animals presents great difficulties. These data obtained *in vivo* in man are most relevant to the whole problem of overcoming the resistance of hypoxic tumour cells and to the different methods such as neutrons and chemical sensitizers now being applied to the problem.

The early anxiety that in some way the appearance of metastasis early in the post-treatment period was increased by hyperbaric oxygen (Johnson, 1967; Wildermuth, 1965) can now be totally dispersed by the exact similarity of the metastasis-free rates in patients treated in oxygen and air now being shown in all the Medical Research Council studies.

We have learned many valuable lessons about the organization of clinical trials in cancer. Trials where patients with advanced disease are included have demonstrated the shortcoming that so many of these patients will inevitably die due to destruction of tissue by tumour and due to distant metastasis that survival figures are insensitive to an improved method. However, a valuable increment in local tumour control may occur although this can only be found by close observations. Such findings encourage the use of new techniques in less advanced cases where a real improvement in survival could occur. We have learned that normal tissue reactions must also be observed with as much care as the local tumour response so as to determine the therapeutic ratio.

The Medical Research Council's trials in hyperbaric oxygen now include over 1500 patients. They represent the vast majority of patients recorded in controlled trials and a considerable percentage of all cases reported in papers concerned with hyperbaric oxygen (Fowler, 1978). The hyperbaric oxygen trials demonstrate the great benefit which results from forming co-operating groups of radiotherapy centres.

The long period of time which these trials have taken has been a cause of concern. Considerable research is required into the conduct of clinical trials in order to see how we can shorten the period before a result is achieved. There is promise that observations of tumour size made at the end of treatment can be correlated with the long-term result in certain types of tumour (Denekamp, 1977; Dische *et al.*, 1978).

The clinical trials of hyperbaric oxygen in radiotherapy have taken many years to mature. At times there has been speculation as to whether any results would emerge. However, the results now reported give them great importance and a distinct place in the history of the treatment of cancer by radiotherapy.

ACKNOWLEDGMENTS

I wish to thank Professor J. F. Fowler and Dr. M. I. Saunders for their advice and encouragement and Mrs. E. Davies for the preparation of the manuscript.

REFERENCES

AITKEN-SWAN, J. and BAIRD, D., 1966. Cancer of the uterine cervix in Aberdeenshire: aetiological aspects. *British Journal of Cancer*, *20*, 642–659.

BENNETT, M. B., SEALY, R. and HOCKLY, J., 1977. The treatment of stage III squamous carcinoma of the cervix in air and hyperbaric oxygen. A preliminary report. Paper presented at the meeting of the British Institute of Radiology, MRC Oxygen Work Party, London on April 14, 1977.

BERRY, G. H., 1978. A clinical appraisal of hyperbaric oxygen in head and neck cancer. *British Journal of Radiology*, *51*, 150.

BRENK Van den, H. A. S., 1968. Hyperbaric oxygen in radiation therapy: investigations of dose-effect relationships in tumour response and tissue damage. *American Journal of Roentgenology*, *102*, 8–26.

CADE, I. S. and MCEWEN, J. B., 1978. Clinical trials of radiotherapy in hyperbaric oxygen at Portsmouth (1964–1976). *Clinical Radiology*, *29*, 333–338.

CADE, I. S., MCEWEN, J. B., DISCHE, S., SAUNDERS, M. I., WATSON, E. R., HALNAN, K. E., WIERNIK, G., PERRINS, D. J. D. and SUTHERLAND, I., 1978. Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the bladder. *British Journal of Radiology 51*, 876–878.

CARLSON, V., DELCLOS, L. and FLETCHER, G. H., 1967. Distant metastases in squamous-cell carcinoma of the uterine cervix. *Radiology*, *88*, 961–966.

CHANG, C. H., CONLEY, J. J. and HERBERT, C., 1973. Radiotherapy of advanced carcinoma of the oro-pharyngeal region under hyperbaric oxygenation. *American Journal of Roentgenology*, *117*, 509–516.

CHURCHILL-DAVIDSON, I., FOSTER, C. A., WIERNIK, G., COLLINS, C. D. PIZEY, N. C. D. SKEGGS, D. B. L., and PURSER, P. R., 1966. The place of oxygen in radiotherapy. *British Journal of Radiology*, *39*, 321–331.

DENEKAMP, J., 1977. Tumour regression as a guide to prognosis: a study with experimental animals. *British Journal of Radiology*, *50*, 271–279.

DISCHE, S., SAUNDERS, M. I. and ANDERSON, P., 1978 (in preparation).

FLETCHER, G. L., LINDBERG, R. D., CADERAO, J. B. and TAYLOR WHARTON, J., 1977. Hyperbaric oxygen as a radiotherapeutic adjuvant in advanced carcinoma of the uterine cervix. Preliminary results of a randomized trial. *Cancer*, *39*, 617–623.

FOWLER, J. F., 1978. Radiobiological considerations from the hyperbaric oxygen trials. A personal view. *British Journal of Radiology*, *51*, 68–69.

GLASSBURN, J. R., DAMSKER, J. I., BRADY, L. W., FAUST, D. S., ANTONIADES, J., PRASAVINICHAI, S., LEWIS, G. C. JR., TORPIE, R. J., and ASBELL, S. O., 1974. Hyperbaric oxygen and radiation in the treatment of advanced cervical carcinoma. In *Fifth International Hyperbaric Congress Proceedings*, *II*, 813–819 (Simon Fraser University).

GLASSBURN, J. R., BRADY, A. W. and PLENK, H. P., 1977. Hyperbaric oxygen in radiotherapy. *Cancer*, *39*, 751–765.

HENK, J. M., KUNKLER, P. B. and SMITH, C. W., 1977. Radiotherapy and hyperbaric oxygen in head and neck cancer. *Lancet*, *ii*, 101–103.

HENK, J. M. and SMITH, C. W., 1977. Radiotherapy and hyperbaric oxygen in head and neck cancer. Interim report of 2nd clinical trial. *Lancet*, *ii*, 104–105.

JOHNSON, R. J. R., 1967. Preliminary observations and results with the use of hyperbaric oxygen and cobalt 60 teletherapy in the treatment of carcinoma of the cervix. *National Cancer Institute Monograph*, *24*, 83–91.

MEDICAL RESEARCH COUNCIL, 1978. A report on the Medical Research Council's Working Party on Radiotherapy and Hyperbaric Oxygen. *Lancet*. (in press).

MOENCH, H. C. and PHILLIPS, T. L., 1972. Carcinoma of the nasopharynx. *American Journal of Surgery*, *124*, 515–518.

MORRISON, R., 1975. The results of treatment of cancer of the bladder—a clinical contribution to radiobiology. *Clinical Radiology*, *26*, 67–75.

PLENK, H. P., 1972. Hyperbaric radiation therapy. Preliminary results of a randomized study of cancer of the urinary bladder and review of the "oxygen experience". *The American Journal of Roentgenology*, *114*, 152–157.

SHIGEMATSU, Y., FUCHIHATA, E., MAKINO, T. and INOUE, T., 1973. Radiotherapy with reduced fraction in head and neck cancer, with special reference to hyperbaric oxygen radiotherapy in maxillary sinus carcinoma. (A controlled study). In *Fraction Size in Radiobiology and Radiotherapy* (edited by T. Sugahara, I. Révész and O. Scott). Tokyo. pp. 180–187.

SHUKOVSKY, L. J., 1970. Dose, time, volume relationships in squamous cell carcinoma of the supraglottic larynx. *American Journal of Roentgenology*, *Radium Therapy and Nuclear Medicine*, *108*, 2–29.

SHUKOVSKY, L. J., 1974. Clinical applications of time-dose data to tumour control. In *Proceedings Conference on the Time-dose Relationships in Clinical Therapy at Madison, October 1974*. Eds. W. L. Caldwell and D. T. Tolbert, pp. 118–150. (Universiry of Winsconsin).

STEWART, J. G. and JACKSON, A. W., 1975. The steepness of the dose response curve both for tumour cure and normal tissue injury. *The Laryngoscope*, *85*, 1107–1111.

WARD, A. J., DIXON, B. and STUBBS, B., 1978. A clinical appraisal of hyperbaric oxygen in cervix cancer (Abstract). *British Journal of Radiology*, *51*, 150–151.

WATSON, E. R., HALNAN, K. E., DISCHE, S., SAUNDERS, M. I. CADE, I. S., MCEWEN, J. B., WIERNIK, G., PERRINS, D. J. D. and SUTHERLAND, I., 1978. Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. *British Journal of Radiology*, *51*, 879–887.

WILDERMUTH, O., 1965. The case for hyperbaric oxygen radiotherapy. *Journal of the American Medical Association*, *191*, 986–990.

1978, *British Journal of Radiology*, *51*, 895–904 NOVEMBER 1978

Vascular permeability in the ears of rats after X-irradiation

By Marilyn P. Law, Ph.D. and R. H. Thomlinson, M. B., B.Chir., F.R.C.R.*

MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W12 0HS

(*Received March, 1978 and in revised form June, 1978*)

ABSTRACT

Late fibrosis in normal tissues is a complication which develops gradually after radiotherapy. It may be related to increase in vascular permeability induced by radiation. Plasma proteins leak into irradiated tissue where fibrinogen may be converted into fibrin which is gradually replaced by fibrous tissue.

Vascular changes in the rat ear were investigated for six months after X-irradiation. Blood volume and vascular permeability were measured *in vivo* by monitoring the radioactivity in both irradiated and control ears after intravenous injection of phosphorus 32 labelled red cells and either iodinated (iodine 125) albumin or fibrinogen.

After a single dose of 40 Gy there was an early increase in vascular permeability to both albumin and fibrinogen. After 20 Gy permeability to albumin was only increased during desquamation but extra-vascular fibrinogen accumulated at earlier times. Extravascular albumin was removed rapidly from irradiated ears, whereas some residual fibrinogen remained. Vascular permeability returned to normal by six weeks and showed no further changes up to six months after irradiation.

Differences between the accumulation of extravascular albumin and fibrinogen at early times after irradiation could be due to some fibrinogen being fixed in the tissue. However, the rat ear showed no late changes comparable to the gradual development of late fibrosis seen in man.

The total dose of radiation which may be used to treat cancer has to be limited because of the reactions which occur in normal tissues included in the field of treatment. Nowadays severe acute reactions are usually avoided but late fibrosis and necrosis may develop gradually to cause symptoms months to years after radiotherapy has been completed.

Necrosis is probably due to ischaemia caused by the fibrotic thickening of the walls of small arteries and arterioles which is characteristic of irradiated tissues at late times after exposure (Wolbach, 1909; Warren, 1942; Rubin and Casarett, 1968; Zollinger, 1970). Fibrosis is the end result of healing processes following injuries which cause cell death. As radiation kills cells, post-irradiation fibrosis might simply be replacement fibrosis resulting directly from cell death (Earlam and Bollinger, 1931; Mohr *et al.*, 1966). However, the histological appearance of tissues damaged by radiation suggests that radiation-induced vascular damage precedes tissue fibrosis (Wolbach, 1909; Jennings and Arden, 1961, 1962; Rubin and Casarett, 1968; Hopewell and Wright, 1970; Ullrich and Casarett, 1977). Depending on the radiation dose, vessels show degenerative changes during the first few weeks which lead to accumulation of oedema fluid and fibrin in the adjacent tissues (Wolbach, 1909; Jennings and Arden, 1961; Rubin and Casarett, 1968; Zollinger, 1970, Fajardo and Stewart, 1971). Later the number of mononuclear cells, including fibroblasts, increases and connective tissue fibres are laid down (Devik, 1955; Jennings and Arden, 1961, 1962; Mostofi *et al.*, 1964; Reed and Cox, 1966; Maisin, 1970; Fajardo and Stewart, 1971). Small foci of oedema and fibrin may persist and the number of mononuclear cells may also be increased suggesting active synthesis of collagen months or even years after exposure (Warren, 1943; Jennings and Arden, 1961, 1962; Reed and Cox, 1966; Mostofi *et al.*, 1964; Fajardo and Stewart, 1971).

These changes are similar to those observed during chronic inflammation in which the development of fibrosis depends on the persistence of exudate and fibrin in the tissue. The similarities between the late radiation response and chronic inflammation suggest the following hypothesis for the pathogenesis of late radiation fibrosis in which exudation of plasma proteins from damaged vessels and deposition of fibrin in the tissue are essential steps.

1. Ionizing radiations have a direct effect on blood vessels, causing an increase in vascular permeability so that plasma proteins leak more rapidly into the tissue (Rigdon and Curl, 1943; Jolles *et al.*, 1961; Shaber and Miller, 1963; Mount and Bruce, 1964; Song *et al.*, 1966).
2. Liquid containing protein which leaks from the blood vessels may accumulate in the tissues as oedema fluid which is rich in fibrinogen, but is eventually cleared by way of the lymphatics.
3. Radiations also cause death of cells; as part of the inflammatory response to this cell death, vascular permeability is increased with the same consequences as those of the direct effect of radiations on blood vessels.
4. Thrombokinase, an enzyme which converts fibrinogen to fibrin, is liberated from cells which die from radiation injury (Peters and Hewitt, 1974). Cells which die in the tissue space do so in an

---

*Present address: Regional Radiotherapy Centre, Mount Vernon Hospital, Northwood, Middlesex.

environment which is rich in fibrinogen and this leads to deposition of fibrin in the tissue.

5. Fibrin deposited in the tissues is "organized" and replaced by fibrous tissue, which may lead to diffuse or localized fibrosis depending on the site of fibrin deposition.

6. As a consequence of the long turnover time of connective tissue cells, there is a prolonged period of cell death so that increased vascular permeability and fibrin deposition continue for long periods of time after irradiation and fibrosis develops gradually.

7. The increase in fibrous tissue, particularly in the walls of small arteries, causes a reduction in the nutritional supply to the tissue. This results in death of parenchymal cells and a continuation of the cycle resulting in fibrosis.

A number of histological observations may be explained by this sequence of events. First, if the hypothesis were correct, the degree of late fibrosis would be related to the extent of fibrin deposition in the tissue. This is the case in the lung where septal and alveolar fibrosis is observed after doses which cause oedema and fibrin deposition at these sites (Jennings and Arden, 1961, 1962; Chandler Smith, 1963) but not if there is no extravasation of fluid (Chandler Smith, 1963; Phillips 1966, Adamson *et al.*, 1970).

Second, the highest concentrations of fibrinogen and thus of fibrin are most likely to occur in the zone just outside the vascular endothelium. For capillaries this zone is in the tissue itself, and interstitial fibrosis does occur in tissues such as the lung and kidney (Jennings and Arden, 1961; Mostofi *et al.*, 1964; Rubin and Casarett, 1968; Aron and Schlesinger, 1974). For larger vessels the zone just outside the endothelium is within the vessel wall and it is the intimal region of arteries and arterioles which is thickened by fibrous tissue so that the lumen is narrowed (Zollinger, 1970).

Third, since the leakage of protein, including fibrinogen, from vessels might in part be determined by the hydrostatic pressure gradient between intra and extravascular compartments, fibrosis might be expected to be more severe where intravascular pressure is greater. Fibrotic changes are more severe in hypertensive than in normotensive individuals (Wilson *et al.*, 1958; Asscher and Anson, 1962; Hopewell and Wright, 1970). The incidence of fibrosis in the walls of arteries rather than in veins (Reinhold, 1974) also supports the concept that there is a relationship between leakage and fibrosis as blood pressure is greater in arteries.

Although histological evidence supports the hypothesis for late radiation fibrosis, each of the stages should be tested experimentally. In the present paper only the early changes are considered. An experimental system was set up to investigate changes in vascular permeability and deposition of fibrin at both early and late times after exposure. To distinguish between increased blood volume and accumulation of extravascular protein, two radioactive tracers were used (Studer and Potchen, 1969; Jones *et al.*, 1970). Red cells labelled with phosphorus 32 were used as the intravascular tracer, while protein, either albumin or fibrinogen, labelled with iodine 125 was used as the permeability indicator. The tissue chosen for the study was the ear (pinna) of the rat, for two reasons. First, the radioactivity in the ear may be measured *in vivo* so that leakage of protein into the tissue space may be followed in one individual animal. Second, changes in an irradiated ear may be compared with the other control ear in each animal, thus reducing the effect of variation between individuals.

Methods

Animals

Male Wistar rats (John's strain) and female CFHB rats were used. The difference in strain had no significant effect on the results. Rats were given potassium iodide (0.25 mg/ml) in their drinking water for one week before injection of labelled proteins to saturate the iodine-binding capacity of the thyroid and ensure rapid excretion of unbound radioiodide. For irradiation and measurement of vascular changes rats were anaesthetized by intraperitoneal injection of sodium amytal, the dose being adjusted for bodyweight and sex (*e.g.* 23.1 mg for a 250 g male, 19.7 mg for a 250 g female).

Radioactive tracers

Sodium phosphate (^{32}P) and iodinated (^{125}I) human albumin and fibrinogen were obtained from the Radiochemical Centre, Amersham. Immunological response to human serum does not occur in small animals until 8–11 days after injection (Weigle and Dixon, 1957; Friedberg, 1960) and therefore HSA has been used to measure vascular permeability in rodents (Song *et al.*, 1966; Chien *et al.*, 1964).

Red blood cells were labelled with ^{32}P after the method of Mollison *et al.* (1958). Blood was obtained from donor rats by cardiac puncture five minutes after intravenous injection of heparin. Approximately 0.6 ml of packed red cells, total radioactivity 2.22 MBq (60 μCi), were suspended in isotonic protein solution for injection.

Iodinated (^{125}I) human serum albumin, protein concentration 20 mg/ml and specific activity 92.5

kBq/mg albumin, was supplied in isotonic solution. 0.7 ml of this solution was added to the labelled red cells to give an iodine activity of approximately 1.11 MBq/ml.

Iodinated (^{125}I) human fibrinogen, specific activity 3.7 MBq/mg fibrinogen, was dissolved in pyrogen-free water as recommended by the Radiochemical Centre, to give an activity of 3.7 MBq/ml in isotonic solution. 0.4 ml fibrinogen solution and 0.3 ml sterile saline were added to labelled red cells to give an activity of approximately 1.11 MBq/ml.

0.9–1.0 ml of double tracer solution containing labelled red cells and iodinated protein (either albumin or fibrinogen) was injected into the tail vein of anaesthetized rats at chosen times after irradiation. Rats were placed in the counting apparatus within 5–10 minutes of injection to determine the radioactivity of each ear. They were re-anaesthetized to estimate the ear radioactivity at later times after injection of the tracers.

Measurement of radioactivity in the rat ear

The probes and analysing system were obtained from J & P Engineering (Reading) Limited. ^{125}I, half life 60 days, 0.035 MeV gamma rays (7%) and 0.027 MeV Te X rays (138%), was detected by an ERD low-energy scintillation probe with a thin sodium iodide crystal (47.5 × 3 mm). ^{32}P, half life 14.3 days, maximum beta energy 1.71 MeV, was detected by a probe with a plastic scintillator (47.5 × 3 mm) designed for beta detection. Each probe was connected to its own analysing system (amplifier, analyser and scaler) so that ^{125}I and ^{32}P could be counted simultaneously. One timer controlled both systems and the total counts on each scaler were printed out automatically.

The anaesthetized rat was placed in a closely fitting cylindrical lead shield. The anterior part of the shield was tapered to fit the head and two holes were cut so that only the ears protruded. The two scintillation probes, shielded by lead collimators, were arranged on a vertical axis with a space between the two crystals. The lead shield containing the rat was held on a cradle which swung about a pivot so that each ear was brought alternately into a horizontal plane between the two counters. The cradle was moved automatically at the end of each counting period. In this way the radioactivity in the irradiated ear could be compared with that in the control ear for each animal. The apparatus was enclosed in a double-walled perspex box and an internal temperature of 28°C was maintained by circulating air over a thermostatically-controlled heating element.

The radioactivity in each ear was measured as the counting rate obtained when each ear was positioned between the probes less the background counting rate obtained when the ears were placed inside the shield. Typically the radioactivity in the ear was 10–15 times background.

The beta detector did not detect a significant number of emissions from ^{125}I, but a correction had to be made for the ^{32}P contribution to the ^{125}I channel using the channels ratio method. ^{32}P labelled red cells were injected into control rats and the ratio (k) of ear counts in the ^{125}I channel (γ_e) to those in the ^{32}P channel (β_e) was calculated. When both isotopes were present the phosphorus contributions to the iodine channel was $k\beta_e$ and the ^{125}I counting rate (I_e) was $\gamma_e - k\beta_e$. The mean value of k for a number of rats, estimated at various times after injection of labelled red cells, was 0.1336 (σ = 0.0156, se = 0.0022).

Irradiation

Ears were irradiated using 250 kV X rays, HVL 1.2 mm Cu, at a dose rate of about 3.8 Gy/min (380 rad/min). Anaesthetized rats were placed on their sides so that only the right ears lay in the vertical collimated X-ray beam. The whole body dose was less than 2% of the dose to the ear. Irradiations were carried out in air at a controlled temperature of 28°C.

Results

Skin reactions

The visible response of the ear was similar to the skin reaction observed in other mammals.

TABLE I

Skin scoring system for rats' ears

0	No visible reaction
1.0	Definite erythema
2.0	Severe erythema
3.0	First sign of breakdown
4.0	Moist desquamation over less than half the outer surface of the pinna, usually covered by a crust.
5.0	Crust over more than half the outer surface.
6.0	Crust over all the outer surface.

For breakdown of the inner surface the following scores are added:

1.0	Crust over less than half the inner surface.
2.0	Crust over more than half the inner surface.
3.0	Crust over all the inner surface.

If the ear is showing signs of dry desquamation (*i.e.* flakiness) 0.5 is added to the erythema score.
The addition of + or − may be given to the score and counts as ±0.33.
The maximum skin score is 9.0.

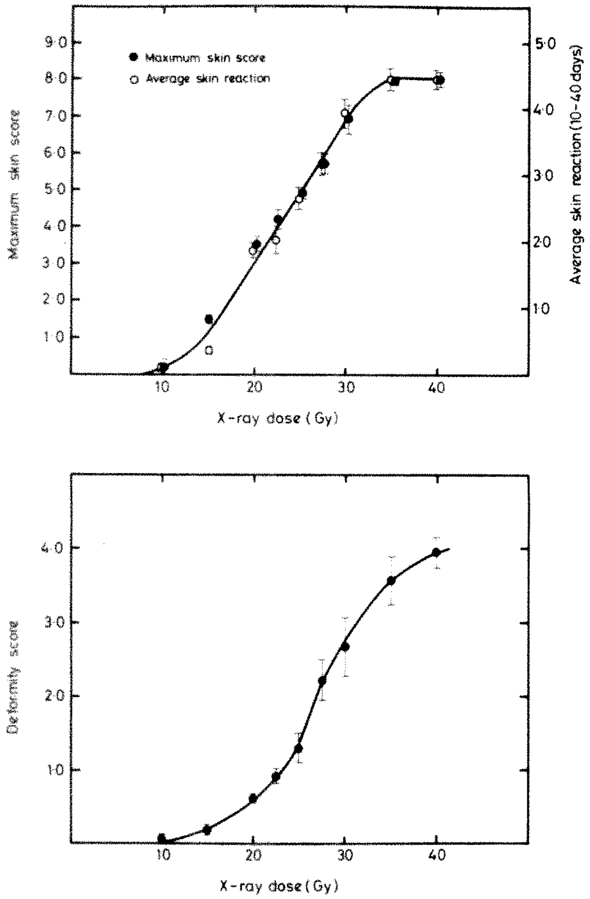


FIG. 1.

The effect of single doses of X rays on the rat ear. Upper diagram: the acute skin reaction expressed as the maximum skin score (●) and as the average skin reaction during 10 to 40 days after irradiation (○). Desquamation occurred after doses of 20 Gy or more.

Lower diagram: the deformity observed during 42–180 days after exposure.

Each point represents the mean for 6–12 rats and standard errors are shown.

Depending on dose, transient erythema developed within the first day, a second wave of erythema began after ten days and was followed by desquamation after doses of 20 Gy or more. After higher doses (more than 30 Gy) a thick crust developed over the entire surface and, as the reaction progressed, the ear decreased in length, the extent of deformity becoming apparent as the skin healed by six weeks. After the acute reaction there were no visible changes in the ears up to ten months after irradiation.

The acute skin reaction was scored daily for 45 days after exposure using the system given in Table I. The response was expressed either as the maximum recorded score or as the average reaction

TABLE II

DEFORMITY SCORES FOR RATS' EARS

0	Normal appearance.
0+, 1−, 1	Degrees of pigmentation and epilation.
1+, 2−	Possible change in shape, edge of pinna frilly.
2.0	Tip of pinna thickened so that pinna is slightly shorter and the edge is puckered.
3.0	Pinna thickened with the tip missing or turned back.
4.0	Pinna thickened and more than half the original length.
5.0	Pinna thickened and less than half the original length.
6.0	Pinna reduced to a stump.
7.0	No pinna.

The addition of + or − counts as ±0.33.

(defined as the area under the response-time curve divided by the time interval) between ten and 40 days after irradiation. Values were computed for each rat and means and standard errors were calculated for each dose. The dose-effect curves plotted by the two methods were similar if an adjustment of scales was made (Fig. 1).

Deformity was scored using the system given in Table II. As deformity did not change during 50–180 days the deformity for each rat was taken to be the mean of all scores for this period. Dose effect curves are shown in Fig. 1.

Vascular changes at early times after irradiation

Figure 2 shows data that were obtained when ^{32}P-labelled red cells and ^{125}I-albumin or ^{125}I-fibrinogen were injected 24 hours after an X-ray dose of 40 Gy. Accumulation and removal of tracers was followed for four days after injection. To evaluate the radiation effect the results were expressed as the ratio of the counting rate for the irradiated ear to the counting rate for the control ear (Fig. 3). For each time of injection mean ratios were calculated using the values for all rats measured at that time.

The use of ^{32}P-phosphate as a red cell label is subject to some uncertainty due to the loss of label from the cells. However, after the injection of ^{32}P-red cells the loss of label from the blood of irradiated and control animals was comparable. Furthermore, irradiation did not change the distribution of phosphate in the ear, as measured by the ^{32}P-ratio (irradiated ear to control ear) after intravascular injection of free ^{32}P-phosphate. Any free ^{32}P-phosphate which leaks out of red cells into tissue, however, would tend to obscure radiation induced

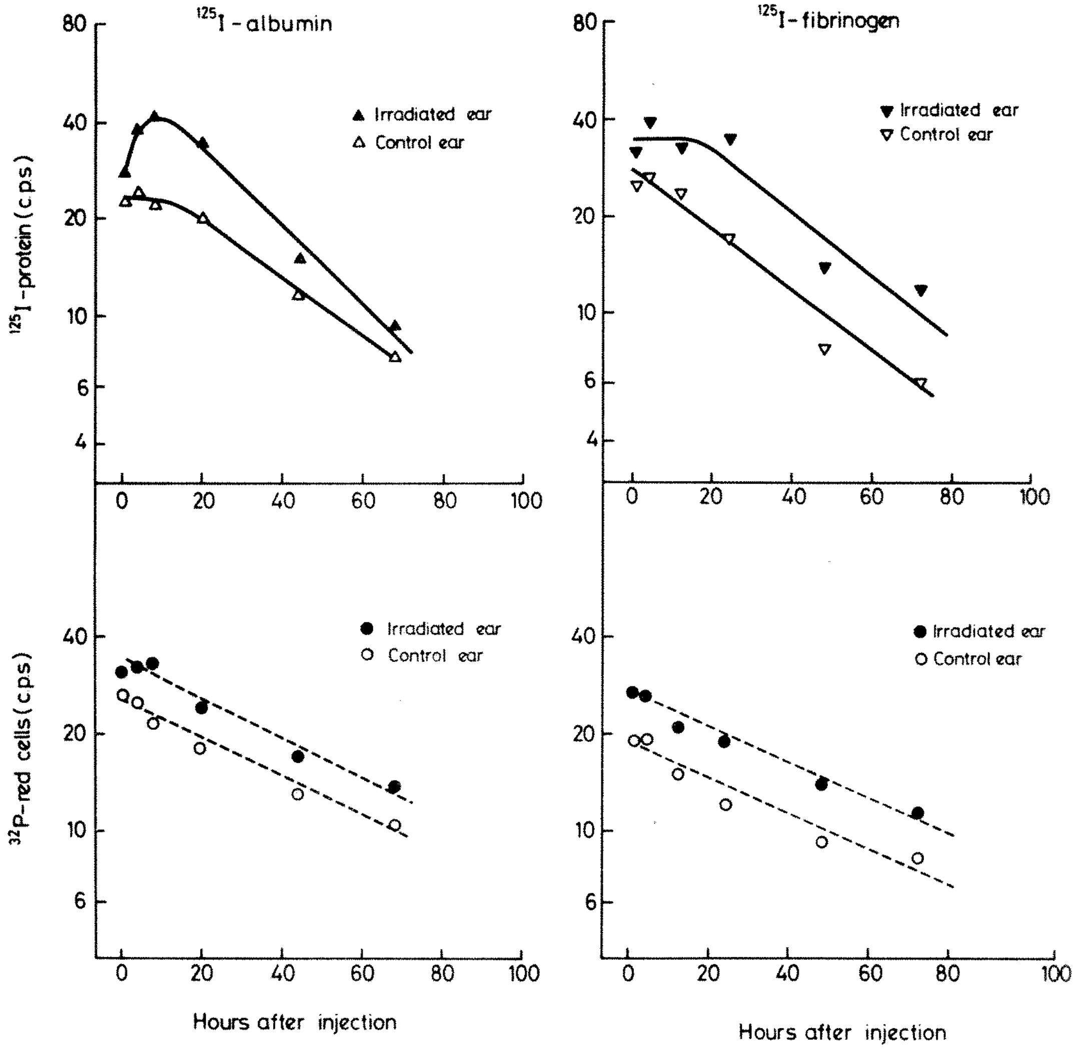


FIG. 2

The accumulation of ^{125}I-protein in the rat ear following injection of tracers 24 hours after a single X-ray dose of 40 Gy to the right ear.

Left hand diagram: The results for one rat which was injected with ^{125}I-albumin and ^{32}P-red cells.

Right hand diagram: The results for another rat which was injected with ^{125}I-fibrinogen and ^{32}P-red cells.

changes in blood volume. Therefore to test the validity of the ^{32}P-red cell ratio as a measure of blood volume changes, a second injection of labelled red cells was given to rats with irradiated ears at different times after the usual injection of labelled red cells and protein. The ^{32}P-ratios before and after the second injection were compared. Up to 24 hours after the first injection the two ratios were not significantly different, but at 48 hours or longer the ^{32}P-ratio before the second injection was lower. These observations indicate that the ^{32}P-ratio is an acceptable measure of blood volume changes during the first 24 hours after injection but gives an underestimate of changes at later times after injection.

Figure 3 illustrates the following points:

1. For both groups of rats relative blood volume, as measured by the ^{32}P-red cell ratio, was increased 24 hours after irradiation.

2. Immediately after injection neither the ^{125}I-albumin ratio nor the ^{125}I-fibrinogen ratio was significantly different from the ^{32}P-red cell ratio, indicating that initially protein was intravascular.

3. Both ^{125}I-albumin and ^{125}I-fibrinogen ratios increased during the first day to values greater than

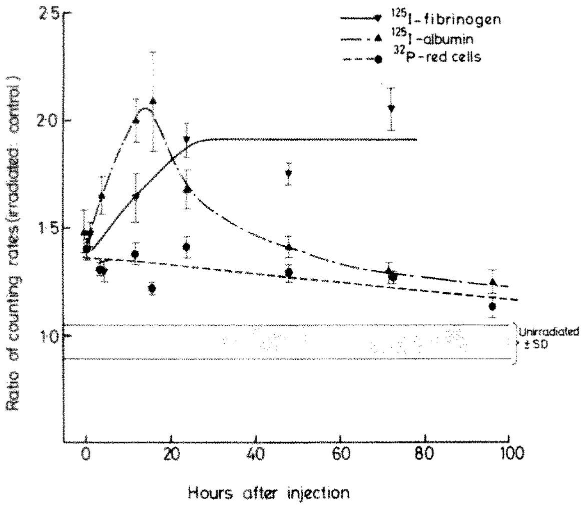


FIG. 3.

The accumulation of ^{125}I-albumin and ^{125}-fibrinogen in irradiated ears relative to control ears following injection of tracers at 24 hours after a single X-ray dose of 40 Gy. Seven rats were injected with ^{125}I-albumin and ^{32}P-red cells and four rats were injected with ^{125}I-fibrinogen and ^{32}P-red cells. Mean ^{32}P-red cell ratios for both groups are plotted.

Vertical lines indicate standard errors.

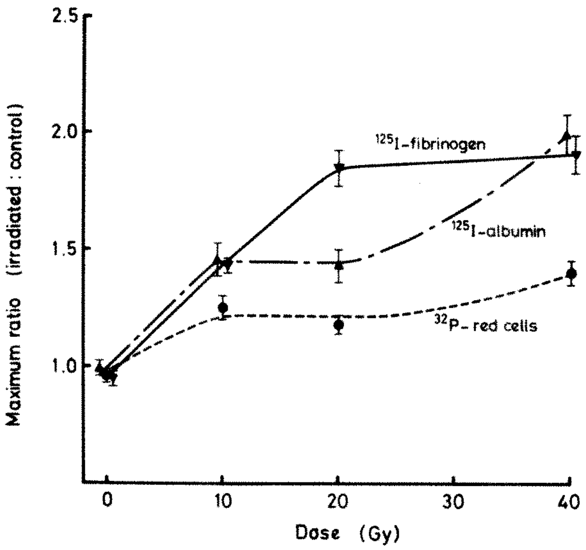


FIG. 4.

Vascular changes at 24 hours after irradiation. Relative blood volume, measured as the ^{32}P-red cell ratio immediately after injection (●), and maximum ratios of counting rates (irradiated: control ear) for ^{125}I-albumin (▲) and ^{125}I-fibrinogen (▼) during the first 24 hours after injection are plotted against the radiation dose.

The difference between maximum ^{125}I-protein ratios and corresponding ^{32}P-red cell ratios is a measure of extravascular protein.

Vertical lines indicate standard errors (4–8 rats).

would be given by changes in blood volume, demonstrating a radiation-induced increase in extravascular protein.

4. After the first day the ^{125}I-albumin ratio decreased and approached the relative blood volume as ^{125}I-albumin was removed more rapidly from irradiated ears than from controls (Fig. 2). The ^{125}I-fibrinogen ratio reached a plateau which did not fall during the time of measurement. The absolute levels of labelled fibrinogen decreased at similar rates in both irradiated and control ears so that there was always an increased amount of fibrinogen, or some derivative of fibrinogen, in irradiated ears relative to control ears.

Dose effect relationships

To obtain some information about dose effect relationships tracers were injected at 24 hours after 10, 20 or 40 Gy. The severity of the vascular response was measured using three parameters: (1) the relative blood volume as measured by the ^{32}P-ratio immediately after vascular mixing, (2) the maximum ratio for albumin, usually observed at 12 hours after injection, (3) the maximum ratio for fibrinogen, usually observed at 24 hours after injection. Dose effect curves are shown in Fig. 4. Blood volume increased with increasing dose. Maximum protein ratios were greater than blood volume increases, indicating an accumulation of extravascular protein. After 10 Gy there was some leakage of both albumin and fibrinogen. After 20 Gy there was no further increase of albumin leakage into the tissue, but a significant amount of extravascular fibrinogen accumulated. After 40 Gy there was a highly significant leakage of both proteins.

Time course of the vascular response

The time course of the permeability response was investigated by injecting tracers at different times after exposure and using the three parameters defined above to indicate the degree of vascular damage. Vascular changes during the first 14 days after 40 Gy are illustrated in Fig. 5. Maximum protein ratios were greater than relative blood volume at all injection times, indicating an accumulation of both extravascular albumin and fibrinogen during the first 14 days after 40 Gy. Blood volume and protein leakage decreased from one day to six days as the early erythema reaction faded and subsequently increased during the main erythema reaction (6–14 days) which precedes desquamation. Vascular changes after 40 Gy were not followed for longer

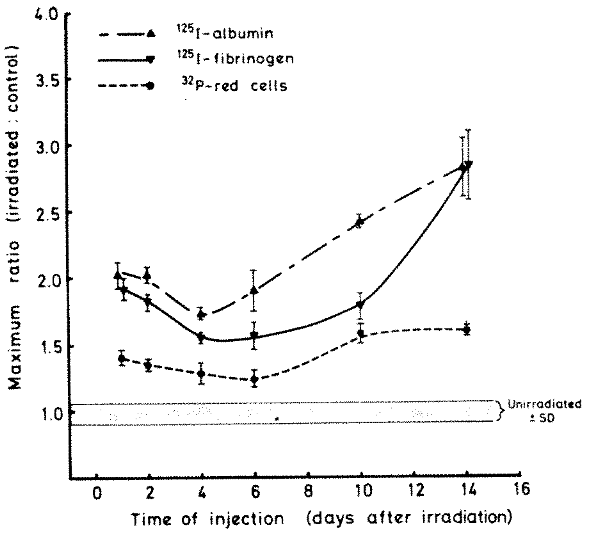


FIG. 5.

The accumulation of ^{125}I-protein in irradiated ears relative to control ears after a single X-ray dose of 40 Gy. Relative blood volume, measured as the ^{32}P-red cell ratio immediately after injection (●), and maximum ratios for ^{125}I-albumin (▲) and ^{125}I-fibrinogen (▼) observed during the first 24 hours after injection are plotted against the time of injection after irradiation. Vertical lines indicate standard errors (3–7 rats).

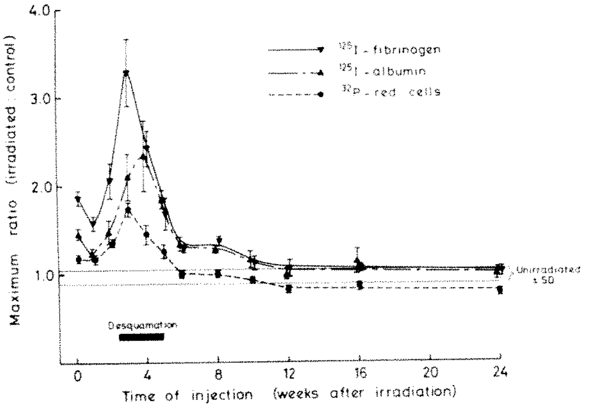


FIG. 6.

The accumulation of ^{125}I-protein in irradiated ears relative to control ears after a single X-ray dose of 20 Gy. Relative blood volume, measured as the ^{32}P-red cell ratio immediately after injection (●), and maximum ratios for ^{125}I-albumin (▲) and ^{125}I-fibrinogen (▼) observed during the first 24 hours after injection are plotted against the time of injection after irradiation. Vertical lines indicate standard errors (3–8 rats).

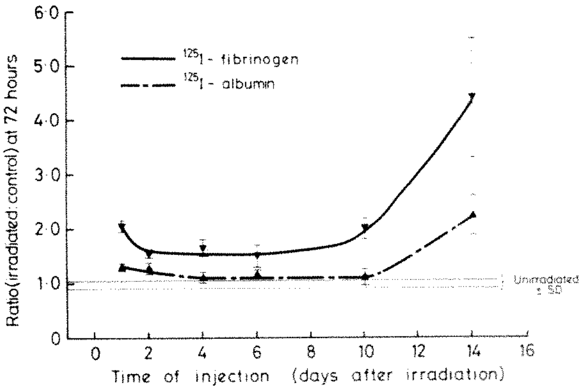


FIG. 7.

The ^{125}I-albumin (▲) and ^{125}I-fibrinogen (▼) content of irradiated ears relative to control ears at 72 hours after injection. Tracers were injected at different times after a single dose of 40 Gy. Vertical lines indicate standard errors (3–7 rats).

times as this dose caused severe desquamation and deformity (Fig. 1).

Figure 6 shows the vascular changes after a single dose of 20 Gy. This dose is comparable to those used in clinical practice and caused mild desquamation but no deformity in the rat ear (Fig. 1). Vascular changes were followed for 24 weeks after irradiation. Both blood volume and extravascular protein were increased at one day after exposure. At one week extravascular fibrinogen but not albumin accumulated. Maximum increases in all three parameters were observed during mild desquamation (three to five weeks), after which blood volume and leakage returned to control values. There was no significant change in vascular permeability after 12 weeks, but there was a suggestion that red cell volume gradually decreased during three to six months.

Removal of extravascular protein

When there is a significant increase in vascular permeability, albumin leaks into the tissue and is rapidly removed, whereas some residual fibrinogen remains in the tissue space (Fig. 3). To illustrate the difference between the removal of extravascular albumin and fibrinogen the albumin ratios and fibrinogen ratios at 72 hours after injection were compared. These ratios are plotted against the time of injection in days after an X-ray dose of 40 Gy in Fig. 7. For all injection times up to and including 14 days albumin ratios at 72 hours after injection were no greater than blood volume changes, indicating that extravascular labelled albumin was removed. Fibrinogen ratios were greater than albumin ratios for all times of injection, suggesting that some residual fibrinogen radioactivity remained in irradiated ears. For injections at 14 days after irradiation the ^{125}I-fibrinogen ratio of about four was due to some radioactivity being fixed as fibrin in the crust which formed during desquamation. Figure 8

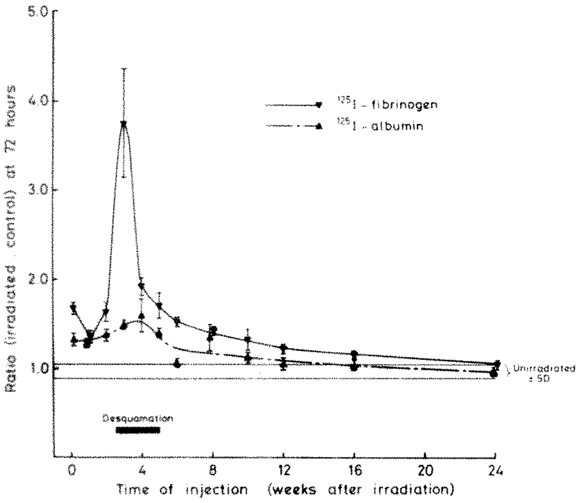


FIG. 8.

The ^{125}I-albumin (▲) and ^{125}I-fibrinogen (▼) content of irradiated ears relative to control ears at 72 hours after injection. Tracers were injected at different times after a single dose of 20 Gy. Vertical lines indicate standard errors (3–8 rats).

illustrates the difference between albumin and fibrinogen removal during 24 weeks after a dose of 20 Gy. The fibrinogen ratio was greater than the albumin ratio after labels were injected one day after irradiation and also two to six weeks after exposure (*i.e.* during desquamation). Although fibrinogen ratios were consistently greater than albumin ratios at later times the difference was not significant.

DISCUSSION

The histological appearance of irradiated tissue suggests that late fibrosis and necrosis may be related to earlier changes in blood vessels. As a consequence of radiation-induced increases in vascular permeability, plasma proteins leak into the tissue where fibrinogen may be deposited as fibrin and subsequently replaced by fibrous tissue. The increase in connective tissue, particularly in the walls of small arteries, may result in ischaemia and cell death which may be followed by replacement fibrosis or by necrosis.

The present results demonstrate radiation-induced changes in the blood vessels of the rat ear. Increases in blood volume during the first six weeks (Figs. 5 and 6) corresponded to the phases of erythema seen during the acute reaction. Similar changes have been reported by other authors (Mount and Bruce, 1964; Song *et al.*, 1966; Song and Levitt, 1970; Hopewell, 1975). After the acute reaction to 20 Gy had healed, the blood volume of the ear tended to decrease to values which were less than normal (Fig. 6). Hopewell (1975) has observed a similar reduction in the blood volume of the hamster cheek pouch after doses of 20 and 30 Gy and the effect may be due to a reduction in the luminal diameter of arterioles (Lindop, 1970; Hopewell, 1975).

Extravascular ^{125}I-albumin was increased at one day after 20 Gy to the rat ear, but not at one or two weeks after exposure (Fig. 6). Extravascular ^{125}I-fibrinogen, however, accumulated at all three times, *i.e.* at one day, one week and two weeks. The greatest increases in ^{125}I-albumin accumulation were observed at three to four weeks, *i.e.* during acute desquamation, although there was wide variation between individuals. Those rats with more severe desquamation showed a larger increase in extravascular ^{125}I-albumin. The greatest accumulation of ^{125}I-fibrinogen was also observed during three to four weeks. This is partly due to fibrin being deposited in the crust. After the acute reactions had healed (at eight to ten weeks) there was no significant extravasation of either protein up to six months after exposure.

The times at which ^{125}I-albumin accumulated after 20 Gy to the rat ear were comparable to those observed by Jolles *et al.* (1961) and by Eassa and Casarett (1973). These authors observed "blueing" after intravenous injection of dye at one day and during the second week after irradiation of rabbit skin. Mount and Bruce (1964), however, suggested that increased uptake of ^{125}I-albumin during the first day was due to increased plasma volume, although the second phase at 14 days was due to leakage of plasma proteins into the tissue. These authors used ^{125}I-diiodofluorescein as a vascular tracer, which may give an overestimate of plasma volume. Song *et al.* (1966) also estimated both blood volume and permeability changes in guinea-pig skin and concluded that the accumulation of protein during the first 24 hours after beta irradiation was due partly to an increase in blood volume but mainly to an increase in vascular permeability.

After 40 Gy, although there was a slight decrease in protein content at four to six days, extravascular protein was always greater in the irradiated ears than in controls. By comparison, in thermal burns the immediate and delayed permeability responses tend to merge as the intensity of the stimulus is increased (Sevit, 1958). Therefore the different patterns of leakage after 20 and 40 Gy are probably a reflection of different degrees of vascular damage. A single dose of 20 Gy is comparable to the doses used in fractionated regimes during radiotherapy and is therefore more relevant to the clinical problem of late fibrosis. After this dose fibrinogen, which has an essential role in the postulated mechanism of radiation fibrosis, accumulated in tissues at times when no significant amount of extravascular albumin was observed.

The accumulation of extravascular ^{125}I-albumin after irradiation could be the result of increased vascular permeability or obstruction of lymph drainage. The lymphatic system seems to be able to withstand high doses of radiation before its function is impaired (Hodes and Griffith, 1941, Engeset, 1964; Ariel *et al.*, 1967; Sherman and O'Brien, 1967). In the present experiments removal of extravascular albumin was more rapid in irradiated ears. Therefore the accumulation of extravascular ^{125}I-albumin after irradiation is probably the result of increased exudation from blood vessels rather than lymphatic obstruction. The absence of an increase in extravascular ^{125}I-albumin during the first two weeks after 20 Gy (Fig. 6) does not necessarily mean that vascular permeability is normal. Extravascular protein will only accumulate in areas of inflammation if the rate of exudation from small blood vessels exceeds the capacity of the lymphatics to remove it.

In the case of ^{125}I-fibrinogen, accumulation of extravascular radioactivity may be due to deposition of ^{125}I-fibrin in the tissue as well as to increased exudation of ^{125}I-fibrinogen. When significant amounts of ^{125}I-fibrinogen are fixed as fibrin in a venous clot the loss of radioactivity from the area of thrombosis is slower than that from the surrounding normal tissue (Hobbs, 1962). In the present experiments, except during moist desquamation, the removal of ^{125}I-fibrinogen from irradiated ears was no slower than that from controls, whereas that of albumin was faster. Since catabolism of labelled proteins occurs in tissues such as the liver, kidney and spleen rather than in the skin (McFarlane 1957, 1963; Campbell *et al.*, 1956; Takeda, 1966; Collen *et al.*, 1972), the loss of extravascular protein radioactivity from the ear must be due to lymph drainage. The increased rate of removal of ^{125}I-albumin from the irradiated ears suggests that there is a radiation effect on lymphatics. If the lymphatic removal of both albumin and fibrinogen are increased the present results are consistent with a small proportion of the fibrinogen radioactivity being fixed in the tissue.

There was no accumulation of extravascular protein after the acute reaction had healed, such as might be expected if there were progressive degeneration of blood vessels during the subclinical phases (Rubin and Casarett, 1968). However, although after higher radiation doses deformity of the ear was observed as soon as the acute reaction healed (two months), there was no change in the proportion nor the total amount of collagen, estimated by a chemical method, in irradiated ears during 6 to 41 weeks after X-ray doses of 30 and 40 Gy (Law, 1977), so further change would not be expected.

CONCLUSIONS

1. It is postulated that late radiation fibrosis may be related to early increases in vascular permeability. Whereas extravascular albumin is removed some fibrinogen may be converted to fibrin in the tissue space and is subsequently replaced by fibrous tissue.
2. The results for the rat ear show that there are differences between the accumulation of extravascular labelled albumin and fibrinogen in irradiated tissue. Extravascular fibrinogen was observed after lower doses of X rays than albumin. Extravascular fibrinogen was observed at earlier times after irradiation than albumin. More fibrinogen than albumin remained in irradiated tissue. These differences are consistent with the hypothesis.
3. Although differences between the accumulation and removal of labelled albumin and fibrinogen in irradiated tissue during the acute reaction may be due to some fibrinogen being fixed in irradiated tissue, ears showed no late changes comparable to the gradual development of late fibrosis seen in normal tissues in man.

ACKNOWLEDGMENT

We would like to thank Mr. R. G. Ahier for his excellent technical assistance.

REFERENCES

ADAMSON, I. Y. R., BOWDEN, D. H., and WYATT, J. P., 1970. A pathway to pulmonary fibrosis: an ultrastructural study of mouse and rat following radiation to the whole body and hemithorax. *American Journal of Pathology*, *58*, 481–498.

ARIEL, I. M., RESNICK, M. I., and OROPEZA, R., 1967. The effect of irradiation (external and internal) on lymphatic dynamics. *American Journal of Roentgenology*, *99*, 404–414.

ARON, B. S., and SCHLESINGER, A., 1974. Complications of radiation therapy: the genitourinary tract. *Seminars in Roentgenology*, *9*, 65–74.

ASSCHER, A. W., and ANSON, S. G., 1962. Arterial hypertension and irradiation damage to the nervous system. *Lancet*, *2*, 1343–1346.

CAMPBELL, R. M., CUTHBERTSON, D. P., MATTHEWS, C., and MCFARLANE, A. S., 1956. Behaviour of ^{14}C and ^{131}I-labelled plasma proteins in the rat. *International Journal of Applied Radiation and Isotopes*, *1*, 66–84.

CHANDLER SMITH, J., 1963. Experimental radiation pneumonitis. *American Review of Respiratory Disease*, *87*, 656–665.

CHIEN, S., SINCLAIR, D. G., CHANG, C., PERIC, B., and DELLENBACK, R. J., 1964. Simultaneous study of capillary permeability to several macromolecules. *American Journal of Physiology*, *207*, 513–517.

COLLEN, D., TYTGAT, G. N., CLAEYS, H., and PIESSENS, R., 1972. Metabolism and distribution of fibrinogen. I. Fibrinogen turnover in physiological conditions in humans. *British Journal of Haematology*, *22*, 681–700.

DEVIK, F., 1955. Study of the local roentgen reaction on the skin of mice, with specific reference to the vascular effects. *Acta Radiologica, Supplementa*, *119*.

EARLAM, M. S. S., and BOLLINGER, A., 1931. Experimental renal disease produced by X ray. *Journal of Pathology & Bacteriology*, *34*, 603–634.

EASSA, E. M., and CASARETT, G. W., 1973. Effect of epsilon-amino-n-caproic acid (EACA) on radiation-induced increase in capillary permeability. *Radiology*, *106*, 679–688.

ENGESET, A., 1964. Irradiation of lymph nodes and vessels. *Acta Radiologica (Stockholm). Supplementa 229*.

FAJARDO, L. F., and STEWART, J. R., 1971. Capillary injury preceding radiation-induced myocardial fibrosis. *Radiology*, *101*, 429–433.

FRIEDBERG, W., 1960. Serum-albumin metabolism in X-irradiated mice with implanted rat bone marrow. *International Journal of Radiation Biology*, *2*, 186–195.

HOBBS, J. T., 1962. External measurement of fibrinogen uptake in experimental venous thrombosis and other local pathological states. *British Journal of Experimental Pathology*, *43*, 48–58.

HODES, P. J., and GRIFFITH, J. Q., 1941. Effect of roentgen irradiation upon lymphatic flow in rats. *Radiology*, *37*, 203–204.

HOPEWELL, J. W., 1975. Early and late changes in the functional vascularity of the hamster cheek pouch after local X-irradiation. *Radiation Research*, *63*, 157–164.

HOPEWELL, J. W., and WRIGHT, E. A., 1970. The nature of latent cerebral irradiation damage and its modification by hypertension. *British Journal of Radiology*, *43*, 161–167.

JENNINGS, F. L., and ARDEN, A., 1961. Development of experimental radiation pneumonitis. *Archives of Pathology*, *71*, 437–446.

1962. Development of radiation pneumonitis: time and dose factors. *Archives of Pathology*, *74*, 351–360.

JOLLES, B., REMINGTON, M., and SIMON-REUSS, I., 1961. Indirect radiation effects and diffusible factors in irradiated tissues. *Acta Radiologica, Therapy, Physics, Biology*, *56*, 57–64.

JONES, T., MORLEY, J., and WILLIAMS, T. J., 1970. Use of radioactive isotopes for continuous recording of increased vascular permeability in the rabbit ear. *Journal of Physiology*, *207*, 10–11P.

LAW, M. P., 1977. Vascular permeability after exposure to X rays and its relation to the late effects of radiation. Thesis submitted to the University of London for the degree of Doctor of Philosophy.

LINDOP, P., 1970. In *Late effects of radiation*. Ed. R. J. M. Fry, D. Grahn, M. L. Griem and J. H. Rust. pp. 79–83. (Taylor and Francis Ltd).

MAISIN, J. R., 1970. The ultrastructure of the lung of mice exposed to a supralethal dose of ionizing radiation on the thorax. *Radiation Research*, *44*, 545–564.

MCFARLANE, A. S., 1957. Use of labelled plasma proteins in the study of nutritional problems. *Progress in Biophysics*, *7*, 115–163.

1963. *In vivo* behaviour of I^{131}-fibrinogen. *Journal of Clinical Investigation*, *42*, 346–361.

MOHR, H. J., MORGENROTH, J., Jr., and SCHNEPPER, K., 1966. The morphological and submicroscopic reaction of guinea pig kidneys during aimed single dose and fractionated roentgen irradiation. *Strahlentherapie*, *129*, 571–585.

MOLLISON, P. L., ROBINSON, M. A., and HUNTER, D. A., 1958. Improved method of labelling red cells with radioactive phosphorus. *Lancet*, *1*, 766–769.

MOSTOFI, F. K., PANI, K. C., and ERICSSON, J., 1964. Effects of irradiation on canine kidney. *American Journal of Pathology*, *44*, 707–719.

MOUNT, D., and BRUCE, W. R., 1964. Local plasma volume and vascular permeability of rabbit skin after irradiation. *Radiation Research*, *23*, 430–445.

PETERS, L. J., and HEWITT, H. B., 1974. Studies on the mechanism of the Révész effect. *British Journal of Radiology*, *47*, 739–740.

PHILLIPS, T. L., 1966. An ultrastructural study of the development of radiation injury in the lung. *Radiology*, *87*, 49–54.

REED, G. B., and COX, A. J., Jr. 1966. The human liver after radiation injury. A form of veno-occlusive disease. *American Journal of Pathology*, *48*, 597–611.

REINHOLD, H. S., 1974. The influence of radiation on blood vessels and circulation. IV. Structural changes in blood vessels. *Current Topics in Radiation Research Quarterly*, *10*, 58–74.

RIGDON, R. H., and CURL, H., 1943. Effect of roentgen irradiation on capillary permeability and inflammation in the skin of the rabbit. *American Journal of Roentgenology*, *49*, 250–257.

RUBIN, P., and CASARETT, G. W., 1968. *Clinical Radiation Pathology*. (W. B. Saunders Company).

SEVITT, S., 1958. Early and delayed oedema and increase in capillary permeability after burns of the skin. *Journal of Pathology & Bacteriology*, *75*, 27–37.

SHABER, G. S., and MILLER, L. L., 1963. Studies on fibrinogen turnover before and after whole body X-irradiation in the rat. *Proceedings of the Society for Experimental Biology and Medicine*, *113*, 346–350.

SHERMAN, J. O., and O'BRIEN, P. H., 1967. Effect of ionizing irradiation on normal lymphatic vessels and lymph nodes. *Cancer*, *20*, 1851–1858.

SONG, C. W., ANDERSON, R. S., and TABACHNICK, J., 1966. Early effects of beta irradiation on dermal vascular permeability to plasma proteins. *Radiation Research*, *27*, 604–615.

SONG, C. W., and LEVITT, S. H., 1970. Effect of X-irradiation on vascularity of normal tissues and experimental tumor. *Radiology*, *94*, 445–447.

STUDER, R., and POTCHEN, E. J., 1969. Transcapillary transport of labeled proteins. I. Regional albumin transfer. *Journal of Nuclear Medicine*, *10*, 442.

TAKEDA, Y., 1966. Studies on the metabolism and distribution of fibrinogen in healthy men with autologous ^{125}I-labelled fibrinogen. *Journal of Clinical Investigation*, *45*, 103–111.

ULLRICH, R. L., and CASARETT, G. W., 1977. Interrelationship between the early inflammatory response and subsequent fibrosis after radiation exposure. *Radiation Research*, *72*, 107–121.

WARREN, S., 1942. Effects of radiation on normal tissues. VI. Effects of radiation on the cardiovascular system. *Archives of Pathology*, *34*, 1070–1079.

WARREN, S., 1943. Effects of radiation on normal tissues. XIII. Effects on the skin. *Archives of Pathology*, *35*, 340–347.

WEIGLE, W. O., and DIXON, F. J., 1957. The elimination of heterologous serum proteins and associated antibody responses in guinea pigs and rats. *Journal of Immunology*, *79*, 23–33.

WILSON, C., LEDINGHAM, J. M., and COHEN, M., 1958. Hypertension following X-irradiation of the kidneys. *Lancet*, *1*, 9–16.

WOLBACH, S. B., 1909. The pathological histology of chronic X-ray dermatitis and early X-ray carcinoma. *Journal of Medical Research*, *21*, 415–449.

ZOLLINGER, H. U., 1970. Die strahlenvasculopathie. *Pathologica Europaea*, *5*, 145–163.

1978, *British Journal of Radiology*, *51*, 905–909 NOVEMBER 1978

The relationship between total dose, number of fractions and fraction size in the response of malignant melanoma in patients

By Shirley Hornsey, D.Sc.

Medical Research Council, Cyclotron Unit, Hammersmith Hospital, London W12 0HS

(*Received December, 1977 and in revised form April, 1978*)

ABSTRACT

The response of melanomas was assessed retrospectively from the clinical notes on 52 patients from three centres in the United Kingdom. The response was very variable. A tentative isoeffect curve was fitted to the UK data which gave a good fit to data from a prospective study from Yale. Clinical data from the Melbourne Clinic on response and fraction size showed a similar reponse to that from the UK and the combined data showed that the response to fraction sizes of 400–800 rad was significantly better (p about 0.01) than to fraction sizes of 200–299 rad.

Malignant melanomas have the reputation of being radioresistant tumours. The response to X-irradiation is variable and unpredictable. Few of these primary tumours are treated in the United Kingdom by radiotherapy and most cases are referred to the radiotherapy clinic when the disease is already widespread.

Cell survival curves obtained *in vitro* from melanoma cells derived from three human malignant melanomas (Barranco *et al.*, 1971) and a rat melanoma (Dewey, 1971) all showed a large shoulder before becoming exponential. These curves indicated that the cells had a large capacity to accumulate and possibly repair sublethal damage and this might explain the reputed radioresistance of some melanomas to fractionated regimes in therapy (Hornsey, 1972a and b). There are other examples of malignant melanoma cells grown *in vitro* which do not show such large shoulders on their survival curves after X-irradiation (Malaise *et al.*, 1975). Such variation between malignant melanoma cell lines may be a factor contributing to the variation in radiation response seen in the human disease.

In a recent prospective study on the "Radiotherapy of Malignant Melanoma", Habermalz and Fischer (1976) have shown, in 13 patients with 44 lesions, that skin metastases do not respond to a fractionation regime with individual doses smaller than 500 rad regardless of the size of the total dose. They also showed that the response of the primary tumours and of metastases in lymph nodes was better after treatment regimes using large doses per fraction and few fractions. These results are consistent with the view that the radioresistance frequently observed clinically may be due to a large capacity to repair radiation damage in the melanoma cells.

In the present study an attempt has been made to obtain data retrospectively from some centres in the UK on the response of malignant melanomas to different fractionation regimes.

CLINICAL MATERIAL

In this retrospective study an assessment has been made of the relationship between number of fractions, fraction size and total dose on the response of melanomas treated at three centres in the UK. Data have been obtained from the registries in Cambridge, Leeds and Liverpool and it has been possible to assess the tumour response in 52 patients (32 female and 20 male) aged between 20 and 90 years old. In four cases concomitant chemotherapy was given and in seven cases radiotherapy followed a partial excision of the tumour. The treatments included orthovoltage and megavoltage X rays and ^{60}Co γ rays. Sites treated were lymph nodes in 32 patients, superficial metastases in three patients, the presumed primary or a recurrence after surgery in 12 patients, and metastases in bone, spine or brain in five patients. The response has been estimated from one to six months after the completion of treatment, using the clinical notes. In the first three sites the assessment of response was based on reduction in size of the lesion and in the last, relief of symptoms (some response). The response was graded into three groups—(1) "no or minimal" response; (2) "some" response, where there was an incomplete reduction in tumour volume; and (3) "good" response where the tumour cleared. The estimate of response is necessarily rather arbitrary; differences in regression rates from one tumour to another, for example, may influence the assessment of response in the early months following treatment. A later assessment could not be made because few patients survived for long periods as the disease was already widespread at the time of treatment.

TUMOUR RESPONSE, TOTAL DOSE AND NUMBER OF FRACTIONS

The response of individual patients is shown in Fig. 1 where the total tumour dose is plotted against the number of fractions. No account has been taken

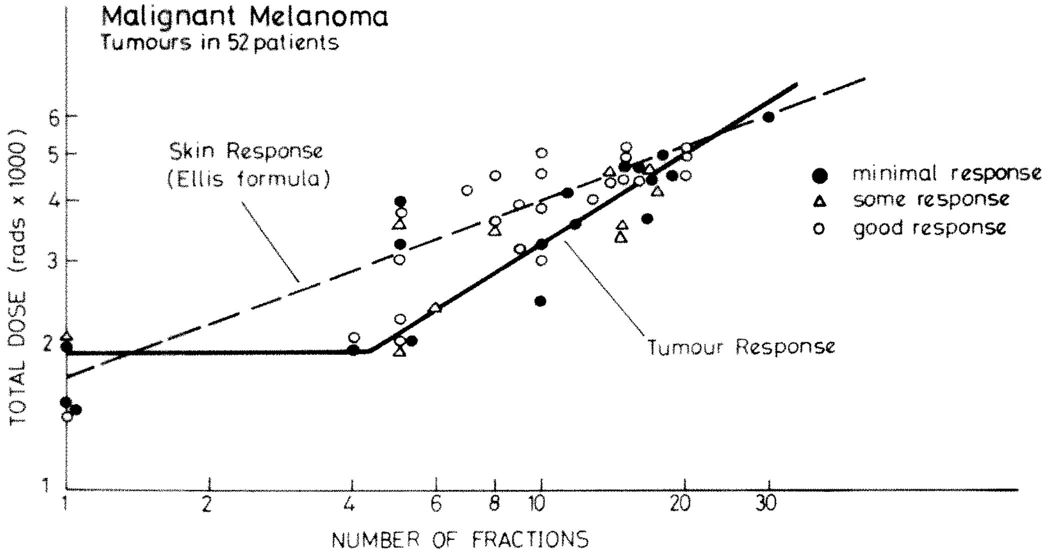


Fig. 1.

The response of malignant melanomas in patients from three centres in the UK to X rays or γ rays showing the relationship between total dose and number of fractions.

TABLE I

Response as a function of total dose

Total dose (rad)	Total tumours	Good or some response
1400–2500	12	7—54%
2500–3500	7	4—57%
3500–4500	18	13—72%
Over 4500	14	9—64%

of overall treatment time or of field size. The response is very variable and there is no unambiguous relationship between total dose, number of fractions and success. In general, greater success is obtained with the higher doses as can be seen from Table I.

An attempt to fit an isoeffect line separating the successes (some or good response) above the line from the failures (no or minimal response) below the line in Fig. 1 has been made by balancing the failures above the line by the successes below the line. From 4 to 30 fractions the seven good responses below the line offset the six poor responses above the line. This line appears to be level between 1 and 4 fractions and then starts to rise. The slope of the proposed isoeffect line from 5 to 30 fractions is considerably greater than that derived by Strandqvist (1944) or Ellis (1969) for skin response. In Fig. 2 the isoeffect curve from the UK data in Fig. 1 is shown in relation to published data on melanoma metastases in lymph-nodes from the prospective study of Habermalz and Fischer (1976). These results are in good agreement with the proposed isoeffect curve from the UK data and add weight to this relationship.

Tumour Response and Fraction Size

The level of tumour response in relation to fraction size is shown in Table II. Also included in Table II are some data, from the Radiotherapy Clinic, Melbourne, of patients with melanoma who were given radical radiotherapy in different fractionation regimes. The data were collected in 1973 by Dr. R. A. Hurley who suggested that there might be a correlation between fraction size and tumour response (personal communication). The responses of the melanomas to dose fractions of different sizes in the two series are remarkably similar. As can be seen, about twice as many tumours show no response after irradiation with 200–299 rad per fraction as after 400–800 rad per fraction (first tumour response column). Also, about twice as many tumours show a good response after irradiation with fractions of 400–800 rad as after fractions of 200–299 rad (last tumour response column) both for the UK and Melbourne.

If the data from the UK and Melbourne are combined for "none" responding tumours and "good" responding tumours for the 200–299 rad per fraction and the 400-800 rad per fraction, a χ^2 test shows that the probability that such an extreme distribution of response might arise by chance is about 0.01.

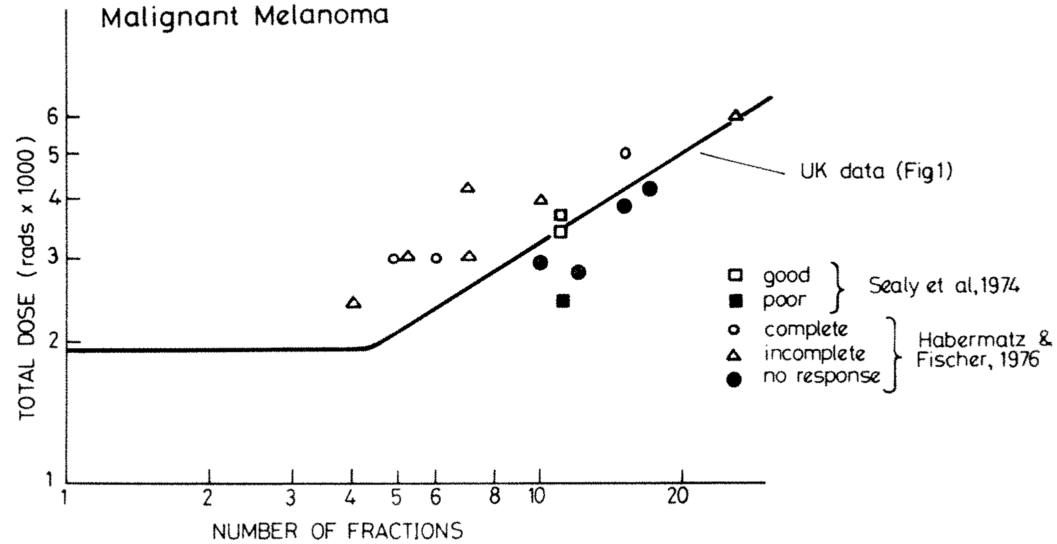


FIG. 2.

The response of malignant melanomas in patients observed in a prospective study by Habermalz and Fischer (1976) and by Seeley *et al.* (1974) shown in relation to the proposed isoeffect curve (Fig. 1) derived from the retrospective study of patients in the UK.

TABLE II

RESPONSE AS A FUNCTION OF DOSE PER FRACTION

Fraction size (rad)		Tumour response			Total tumours
		None	Some	Good	
200–299	UK	6—46%	4—31%	3—23%	13
	Mel.	7—47%	5—33%	3—20%	15
300–399	UK	5—33%	1—7%	9—60%	15
	Mel.	2—14%	5—36%	7—50%	14
400–800	UK	4—21%	4—21%	11—58%	19
	Mel.	3—17%	6—33%	9—50%	18

DISCUSSION

It is possible that hypoxia might contribute to the reputed insensitivity of melanomas to radiation. Improved response has been observed under hyperbaric oxygen though the results could have been due to the larger fractions used, 450–500 rad per fraction (Sealy *et al.*, 1974). Where the response of tumours is influenced by the presence of hypoxic cells it would be expected that the isoeffect curve relating total dose and number of fractions would dip or be flat over low fraction numbers as the increased dose required due to fractionation is counterbalanced by the increase in sensitivity due to reoxygenation (Elkind *et al.*, 1968; Howes and Field, 1968). This is seen in Figs. 1 and 2. The length of this initial flat response in the isoeffect curve may give some indication of the degree of hypoxia in the tumours. From the present data the rise in the isoeffect curve begins at 4–5 fractions. This is a greater number of fractions than that noted by Howes and Field (1968) from the data of Friedman and Pearlman on the response of breast nodules in patients, when the rise began at 2–3 fractions. This suggests that hypoxia in melanomas may be greater or resolve more slowly than in breast nodules and that some of the poor responses observed in melanomas treated with a few large fractions may be due to hypoxia. It has been shown by Guichard *et al.* (1977) that a human melanoma cell line transplanted into athymic nude mice contained a larger fraction of hypoxic cells in the resulting tumour than many other tumour lines grown in athymic nude mice. However, another melanoma line grown *in vivo* had a relatively small fraction of hypoxic cells (Hill and

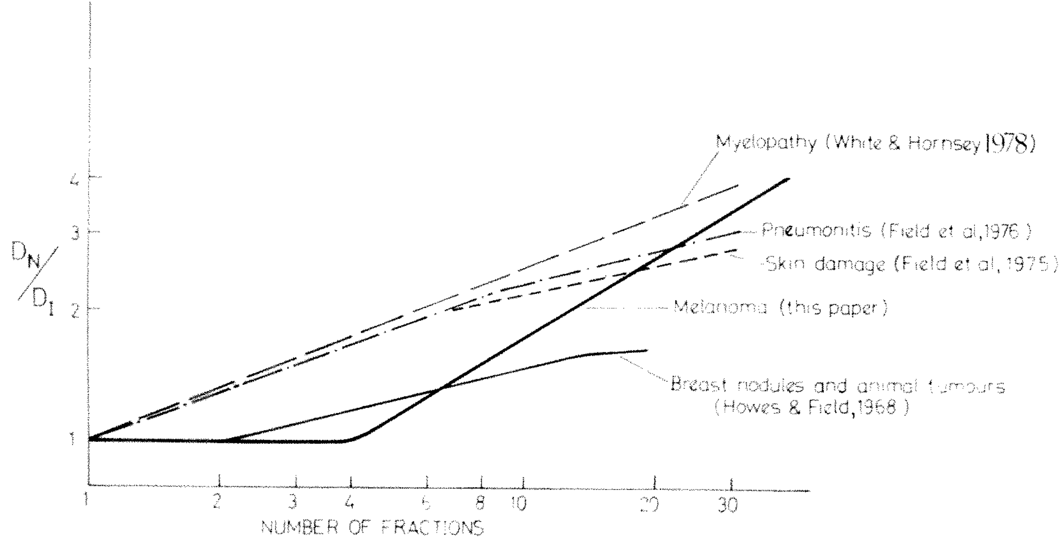


Fig. 3.

The isoeffect curve for malignant melanomas compared with isoeffect curves for some limiting normal tissues and for breast nodules. D_N is the total dose given in N fractions and D_1 is the single dose for the same effect.

Stanley, 1975), so the level of hypoxia appears to be a rather variable factor from one melanoma to another and may be another reason contributing to the considerable variation in response seen in human melanomas.

The steep rise of the proposed isoeffect curve for the response of melanomas is greater than that shown by Howes and Field (1968) for the response of breast nodules and animal tumours. The isoeffect curve for melanoma response is also steeper than the isoeffect curves for early or late skin damage (Douglas and Fowler, 1976; Field *et al.*, 1975) or for the induction of radiation pneumonitis (Field *et al.*, 1976) or radiation myelopathy (White and Hornsey, 1978) as can be seen in Fig. 3. As some of the isoeffect curves in Fig. 3 were from animal data in which the absolute dose is not applicable to patients the curves have been normalized by plotting D_N/D_1 against number of fractions. The steeper isoeffect curve for response of melanomas than for many normal tissues means that the tumour will be spared damage to a greater extent than normal tissues by increasing the fractionation of dose. A balance is needed between sufficient fractionation of dose to overcome the problems of hypoxia in the tumour and reduction in the number of fractions to reduce the larger degree of sparing of damage to the tumour by fractionation. From the data presented in Figs. 1 and 2 and from the observations of Sealy *et al.* (1974) a balance seems to be in the range of 6–10 fractions of 500–600 rad where the limiting normal tissues would allow. The relationship of these doses to skin tolerance can be seen in Fig. 1 where the skin tolerance curve is drawn from the Ellis formula (1969). At lower doses per fraction and higher numbers of fractions the skin tolerance and tumour response curves converge.

The results, limited as any retrospective survey must be, do add strong support to the view that a better prognosis after the localized treatment of melanomas by radiotherapy is obtained when relatively few large fractions are used rather than a large number of small fractions. A significant difference (p about 0.01) in response was observed between fraction sizes of 200–299 rad compared with 400–800 rad, the latter giving the better response.

The steep isoeffect curve for response of melanomas is indicative of cells with a large capacity to repair sublethal damage, and suggests that therapeutic benefits may be obtained by using concomitant treatments which reduce this repair capacity, such as neutrons, hyperthermia or some drugs. Other methods which may be used to overcome the suggested problem of hypoxia, such as irradiation with neutrons, may also have the added advantage of reducing the capacity for repair following irradiation.

Conclusion

The data in this retrospective study add support to data from the prospective study of Habermalz and Fischer (1976) and indicate that a possible improvement in the localized treatment of melanoma may be gained by using a small number of large doses. Techniques aimed at reducing hypoxia and reducing repair between fractions during treatment may give a large therapeutic gain.

ACKNOWLEDGMENTS

It is a pleasure to thank Prof. N. M. Bleehen and Dr. P. N. Plowman, Prof. C. A. Joslin and Mr. P. J. Corbett, Dr. K. Ryall and Dr. R. A. Hurley for their help in obtaining and processing the clinical data from their centres at Cambridge, Leeds, Liverpool and Melbourne, and to thank the consultant clinicians at these centres for contributing their data and consenting to its use; also to acknowledge the help from the staff of the Registries at these centres. I am grateful to Dr. D. K. Bewley for help with statistics.

REFERENCES

BARRANCO, S. C., ROMSDAHL, M. M. and HUMPHREY, R. M., 1971. The radiation response of human malignant melanoma cells grown *in vitro*. *Cancer Research*, *31*, 830–833.

DEWEY, D. L., 1971. The radiosentitivity of melanoma cells in culture. *British Journal of Radiology*, *44*, 816–817.

DOUGLAS, B. G., and FOWLER, J. F., 1976. The effect of multiple small doses of X rays and a basic interpretation. *Radiation Research*, *66*, 401–426.

ELLIS, F., 1969. Dose, time and fractionation: a clinical hypothesis. *Clinical Radiology*, *20*, 1–8.

ELKIND, M. M., WITHERS, H. R., and BELLI, J. A., 1968. Intracellular repair and the oxygen effect in radiobiology and radiotherapy. In *Frontiers in Radiation Therapy and Oncology*, *3*, p. 55. Ed. J. M. Vaeth, Krager, Basel.

FIELD, S. B., HORNSEY, S., and KUTSUTANI, Y., 1976. Effects of fractionated irradiation on mouse lung and a phenomenon of slow repair. *British Journal of Radiology*, *49*, 700–707.

FIELD, S. B., MORRIS, C., DENEKAMP, J., and FOWLER, J. F., 1975. The response of mouse skin to fractionated X rays. *European Journal of Cancer*, *11*, 291–299.

GUICHARD, M., GOSSE, C., and MALAISE, E.-P., 1977. Survival curve of a human melanoma in nude mice. *Journal of the National Cancer Institute*, *18*, 1665–1669.

HABERMALZ, H. J., and FISCHER, J. J., 1976. Radiation therapy of malignant melanoma. Experience with high individual treatment doses. *Cancer*, *38*, 2258–2262.

HILL, R. P., and STANLEY, J. A., 1975. The response of hypoxic B16 melanoma cells to *in vivo* treatment with chemotherapeutic agents. *Cancer Research*, *35*, 1143–1153.

HORNSEY, S., 1972a. The radiation response of human malignant melanoma cells *in vitro* and *in vivo*. *Cancer Research*, *32*, 650–651.

1972b. The radiosentitivity of melanoma cells in culture. *British Journal of Radiology*, *45*, 158.

HOWES, A. E., and FIELD, S. B., 1968. The oxygen effect: a new look at "Friedman and Pearlman". *British Journal of Radiology*, *41*, 554–555.

MALAISE, E. P., WEININGER, J., JOLY, A.-M., and GUICHARD, M., 1975. Measurements *in vitro* with three cell lines derived from melanoma. In *Cell Survival after low Doses of Radiation: Theoretical and Clinical Implications*. pp. 223–225, ed. T. Alper. Pub. Institute of Physics and John Wiley, London.

SEALY, R., HOCKLEY, J., and STEPSTONE, B., 1974. The treatment of malignant melanoma with cobalt and hyperbaric oxygen. *Clinical Radiology*, *25*, 211–215.

STRANDQVIST, M., 1944. Studien über die kumulative Wirkung der Röntgenstrahlen bei Fractionierung. *Acta Radiologica, Supplement 55*.

WHITE, A., and HORNSEY, S., 1978. The effect of single and fractionated X rays on damage to the rat spinal cord. *British Journal of Radiology*, *51*, 515–523.

1978, *British Journal of Radiology*, *51*, 910–912

Technical note

Preparation of the colon prior to radiology—a comparison of the effectiveness of castor oil, Dulcodos and X-Prep liquid

By A. Cargill, M.R.C.P.U.K., D.M.R.D., and W. Hately, F.R.C.P.Ed., F.R.C.R.

Department of Diagnostic Radiology, London Hospital, Whitechapel, London E1 1BB

(*Received January, 1978 and in revised form June, 1978*)

Diagnostic accuracy in abdominal X-ray examination is dependent upon thorough elimination of faecal residues and fluid from the colon (Templeton, 1963; de Lorimier and Hanna, 1956). Repeat procedures due to unsatisfactory preparation are costly in materials and put increased demands on the time of the radiologist and his staff. They are also distressing for the patient and indeed potentially hazardous for the elderly (Berman, *et al.*, 1965).

Various routines for preparation of the large bowel prior to radiological examination are in use employing a wide range of laxatives, sometimes in combination with colonic lavage. Often these regimens have come to be accepted by time hallowed tradition and in some cases they are tolerated as barely satisfactory, rather than by any claim to excellence. It therefore seemed worthwhile to carry out a critical appraisal of the methods used in the authors' department, with particular reference to the technical quality of the film obtained and patient acceptance.

Three laxatives were examined in the present study; castor oil, Dulcodos and X-Prep liquid. Castor oil and Dulcodos are currently in use in The London Hospital for preparation prior to barium enema and intravenous urographic examinations respectively. It was also decided to include X-Prep liquid since it has been reported as a highly effective and acceptable bowel evacuant (Campbell, 1972; Dickie *et al.*, 1970). Castor oil is widely used on account of its low cost. It acts by its irritant effect on the small intestine after hydrolysis to ricinoleic acid (Laurence, 1973). Many patients find it objectionable to take and it has been associated with a high occurrence of fictitious polyps necessitating re-examination (Yates, *et al.*, 1950). Dulcodos contains both bisacodyl which directly stimulates sensory recaptors in the lumen of the colon (Laurence, 1973), and a faecal softener, di-octyl sodium sulphosuccinate. X-Prep liquid contains a standard extract of senna. Soluble anthroquinone derivatives present in the sennosides are absorbed in the small intestine and later are excreted into the colon where they act along with those that have escaped absorption. They are probably modified by bacterial action before they can initiate peristalsis (Laurence, 1973).

METHOD

One hundred consecutive patients (either in-patients or out-patients) referred for barium enema examination were allocated randomly to either castor oil or X-Prep liquid. Those that were given castor oil were instructed to take 25 ml on an empty stomach at midday on the day prior to examination. The X-Prep liquid patients were told to take 71 ml (containing the equivalent of 142 mg sennosides A and B) of the chocolate-flavoured liquid on the evening before examination.

A further 100 consecutive patients were randomly allocated to either Dulcodos or X-Prep liquid, prior to intravenous urography. The Dulcodos group were told to take two tablets (each containing 5 mg bisacodyl and 100 mg di-octyl sodium sulphosuccinate) on the night before examination and also on the preceding night. The X-Prep liquid patients were again given 71 ml on the night preceding examination.

None of the 200 patients were given washouts before the preliminary films, which were, of necessity, taken at varying times between 9.00 a.m. and 4.00 p.m. depending on the patient's appointment.

For two days before a barium enema examination patients were instructed to eat only a light diet consisting of eggs, cheese, white bread and butter with no vegetables, fruit, salads or brown bread. On the morning of the examination the patient was asked to take only a light meal of tea, toast with jam or a biscuit.

During the day before an intravenous urogram the patient was instructed not to eat any fruit, salads, green vegetables or brown bread. On the morning of the examination the patient was allowed a slice of dry toast or biscuits.

The control films of the abdomen were examined by two radiologists who were unaware of the identity

TABLE I

RESULTS OBTAINED COMPARING X-PREP LIQUID AGAINST CASTOR OIL IN THE PREPARATION OF PATIENTS FOR BARIUM ENEMA EXAMINATION

		Excellent	Good	Poor	Volunteered side effects	Elicited side effects
X-Prep	In-patient	8	7	8	Slight griping 1	Pain 1
	Out-patient	18	6	3	Mild cramp 1	Nausea 2 Mild griping 4
	TOTAL	26	13	11	2	7
Castor oil	In-patient	3	2	18	Slight griping 1	Pain 2 Cramp 1
	Out-patient	9	7	11	Nausea 1	Nausea 2 Pain 2
	TOTAL	12	9	29	2	7

TABLE II

RESULTS OBTAINED COMPARING X-PREP LIQUID AGAINST DULCODOS IN THE PREPARATION OF PATIENTS FOR INTRAVENOUS UROGRAPHY

		Excellent	Good	Poor	Volunteered side effects	Elicited side effects
X-Prep	In-patient	6	9	2	Nil	Mild pain 2
	Out-patient	20	7	6	Slight griping 3 Slight pain 1 Nausea/Vomiting 3	Griping 4 Colicky pain 4
	TOTAL	26	16	8	7	6
Dulcodos	In-patient	3	6	11	Pain 1	Pain 1
	Out-patient	11	10	9	Severe griping 1 Slight griping 1 Moderate pain 1 Feeling weak 1	Pain 2
	TOTAL	14	16	20	5	3

of the laxative used and classed as:

Excellent: no gas or faecal residues;

Good: minimal residues with no obscuring of detail;

Poor: marked residues or gas obscuring detail.

RESULTS

Results by type of examination and laxative are shown in Tables I and II. It can be seen that both the barium enema and the intravenous urography patients gave a substantially higher proportion of good and excellent results when prepared with X-Prep, than when castor oil or Dulcodos was used. A chi square test shows the difference between X-Prep liquid and castor oil is highly statistically significant ($\chi^2=13.98$ (2 d.f) $0.01>p>0.001$) and the difference between X-Prep liquid and Dulcodos is statistically significant ($0^2=8.77$ (2 d.f) $0.02>p>0.01$).

Results obtained with out-patients were generally better than those with in-patients, irrespective of the laxative used. This is probably accounted for by loss of regularity of bowel function in hospitalized patients.

In the intravenous urography group, seven patients taking X-Prep liquid reported side effects and a further six mentioned side effects when questioned. Comparative figures for the patients taking Dulcodos are five reports of side effects and a further three patients mentioning side effects on questioning.

In the barium enema group, two patients reported side effects after taking X-Prep liquid and two after castor oil. Questioning elicited side effects in a further seven patients taking X-Prep liquid and seven after castor oil. None of the side effects were serious and all were obviously related to the action of the laxative on the bowel (*e.g.* colicky pain, griping).

Conclusion

Of the three preparations examined, X-Prep liquid was found to give the best preparation of the colon in the doses used and was also most acceptable to the majority of the patients, particularly when compared with castor oil. Side effects were encountered with all three preparations, but none were serious and no agent was associated with a greatly reduced incidence of griping and colic. It would therefore seem that in the context of the present study, X-Prep liquid is the preferred medium for preparing the bowel prior to radiological examination of the abdomen.

Acknowledgments

We are very grateful to Dr. Chaput de Saintonge of the Department of Pharmacology, London Hospital Medical College, for his help and advice in the preparation of this paper. We should also like to thank Napp Laboratories Limited for the supply of X-Prep liquid.

REFERENCES

Berman, C. Z., Jacobs, M. G., and Bernstein, A., 1965. Hazards of the barium enema examination as studied by electrocardiographic telemetry: preliminary report. *Journal of American Geriatrics Society*, *13*, 672–686.

Campbell, J. S., 1972. Bowel evacuation prior to abdominal roentgenography. *Clinical Trials Journal*, *9*, 29–31.

de Lorimier, A. A., Moehring, H. G., and Hanna, J. R., 1956. The digestive tract, the gall bladder, liver and pancreas, the excretory tract and special studies emphasizing differential considerations. *Clinical Roentgenology*, *Vol. IV*, p.9. (The Ryerson Press, Toronto.)

Dickie, J., James, W. B., Hume, R., and Robertson, D., 1970. A comparison of three substances used for bowel preparation prior to radiological examination. *Clinical Radiology*, *21*, 201–202.

Laurence, D. R., 1973. *Clinical Pharmacology*, *21*, 9–21.14. (Churchill Livingstone, Edinburgh.)

Templeton, F. E., 1963. Errors in the radiological diagnosis of gastrointestinal lesions. In *Current Gastroenterology*. Edited by McHardy, J. (G. Harper and Bros., N.Y.)

Yates, C. W., Moreton, R. D., and Cooper, E. M., 1950. Double-contrast studies of the colon with special reference to preparation and fictitious polyps. *Radiology*, *55*, 539–544.

Book review

A Practical Approach to Modern X-ray Equipment. By T. T. Thompson, pp. xvii+233, illus., 1978 (Massachusetts, USA; Little, Brown & Co.), $11.50.

This book, as the title suggests, is a "down to earth" approach to modern X-ray equipment and accessories from the users point of view. Written primarily for radiologists, in a most readable style it explains, in non-mathematical language, the basic elements and principles of the equipment encountered in a diagnostic radiology department. This is not an "in-depth" reference book on X-ray equipment; rather it has been written to give sufficient background information to prepare a user for making reasonable, informed decisions about what he needs and what he should buy. The cost implications of the various choices have also been included, an aspect often ignored in the scientific and technical literature.

Each chapter presents a major component of radiographic equipment, describing the basic principles of operation and construction, the variations encountered, and the significance within the complete system. There is an emphasis on the need for quality control and maintenance and a final chapter which will be a most helpful guide when purchasing equipment. It is entitled "Bid and Performance Specifications and Warranty and Service Contracts". It contains a list of some 20 items whose specifications should be checked, and provides the user with a guide as to what tolerances many of these should have.

Throughout the book Dr. Thompson has drawn attention to the everyday problems most likely to be encountered with the various pieces of equipment in a radiology department and has described the probable causes and solutions. Another useful feature is that when fresh terminology is introduced, it is printed in italics and defined. This is particularly helpful in the chapter on computed tomography where a considerable number of new terms have been introduced recently into the radiology vocabulary.

In summary, this is a book for the user wishing to know how his equipment works but not in too great detail. The style is conversational and in parts a little patronising. On the whole it is a book well worth having on the bookshelves to accompany the more scientific and technical literature.

S. C. Lillicrap.

1978, *British Journal of Radiology*, *51*, 913–914

Case reports

Non-thrombotic occlusion of the cavernous carotid from subdural empyema

By R. W. Katzberg, M.D.* and G. Griffiths, M.B., B.C.H., D.C.H., F.R.C.R.†

Department of Diagnostic Radiology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642.

(*Received August, 1976 and in revised form April, 1978*)

Scattered reports of the significant angiographic findings in intracranial bacterial infection have demonstrated several types of vascular changes, many of which are non-specific. These include narrowing or spasm of the major vessels at the base of the brain, segmental arterial dilatation, peripheral arterial occlusions, aneurysmal formation due to vessel wall involvement by infection, arterio-venous shunting and a thickened vascular wall of the dura (Ferris *et al.*, 1968). The angiographic appearance of narrowing of a vessel may result from cellular infiltration, oedema of the wall, extrinsic compression or irritability of the vessel wall with actual vasospasm (Ferris and Levine, 1973). Progression of these changes to non-thrombotic occlusion has been observed in the smaller arteries of the brain. This is the first case demonstrating radiographic and pathologic documentation of non-thrombotic occlusion of the internal carotid artery secondary to intracranial infection.

CASE HISTORY

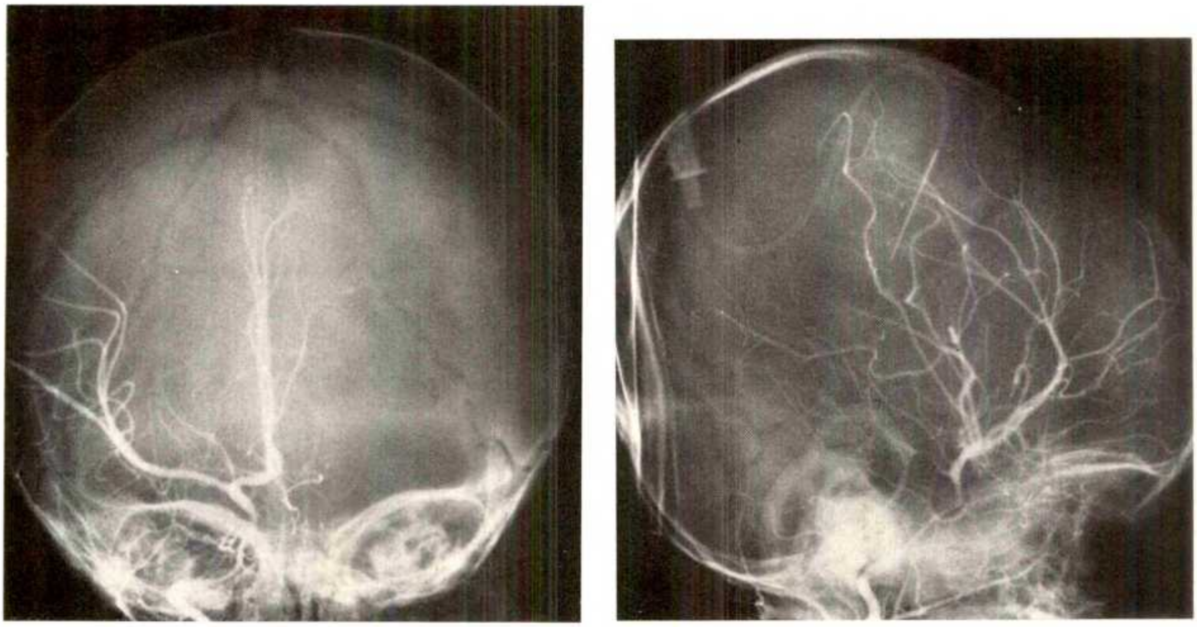
A nine-month old female infant was admitted to Strong Memorial Hospital with a seven day history of upper respiratory infection, fever, and a purulent discharge from the left external auditory canal. Physical examination disclosed oedema of the left side of the head, a right central eighth nerve palsy and a right hemiparesis, which developed into decerebrate posturing. A left subdural tap showed clear cerebrospinal fluid under no pressure. There was no growth on culture of the blood, cerebrospinal fluid or ear drainage, but gram positive micrococci were noted in the latter.

An angiogram showed no internal cerebral circulation to the left hemisphere after a left common carotid injection. A

---

*Present address: Wilford Hall, USAF Medical Center/ SGHR Lackland AFB, Texas 78236.

†Present address: Department of Radiology, Royal Gwent Hospital, Newport, Gwent.



A

B

FIG. 1.

(A) Anteroposterior and (B) lateral subtraction views following a right common carotid injection showing a long segment of severe narrowing of the cavernous portion of the internal carotid artery.

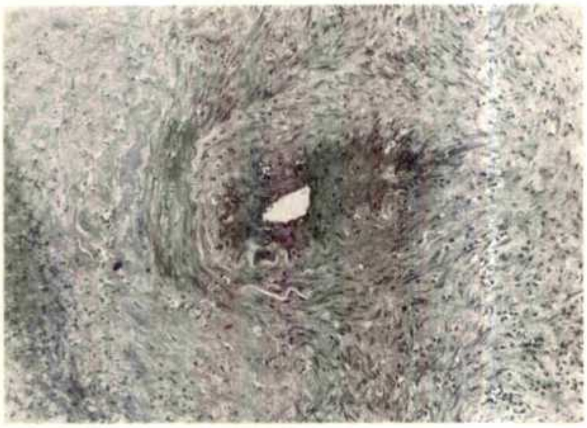


FIG. 2.

High power photomicrograph of the left cavernous carotid artery which shows marked luminal narrowing associated with mild intimal thickening and polymorphonuclear cells in the adventitia.

long segment of severe narrowing affecting mainly the cavernous portion of the right internal carotid artery was also demonstrated (Fig. 1). The circulation time was markedly prolonged.

The patient continued to deteriorate and the following day had a cardiac arrest and died.

At post-mortem examination a subdural empyema of the left middle cranial fossa was found with bilateral septic thrombosis of the cavernous sinuses resulting from a left otitis media and acute osteomyelitis of the left petrous bone. Microscopy demonstrated severe stenosis of the left cavernous carotid artery without thrombosis and with polymorphonuclear infiltration of the adventitia (Fig. 2), The intima was slightly thickened and the vascular lumen measured 66 microns. The lumen of the right cavernous carotid artery was 600 microns in diameter with focal intimal thickening and acute and chronic peri-adventitial inflammation.

DISCUSSION

Subdural empyema has become a relatively rare intracranial suppurative disease with the advent of antibiotics. The mortality rate has dropped from nearly 100% to a current rate of 30% (Bhandari and Sarkari, 1970). Paranasal sinus infections are now the most common source followed by otitis media. Non-haemolytic streptococcus is the most frequent offending organism (Bhandari and Sarkari, 1970). Subdural empyema is a surgical emergency and early diagnosis vital.

Vascular spasm frequently observed with intracranial bacterial infection presumably is the result of irritation to the arterial wall from the surrounding inflammatory material, causing luminal narrowing (Ferris *et al.*, 1968). Structural changes result from inflammatory involvement of the vessel wall itself with resultant intimal proliferations and inflammatory cells in all layers (Greitz, 1964). There are variable degrees of fibrosis with acute and chronic cellular infiltrates in the subarachnoid space. Progressive narrowing of the lumen leads to thrombosis with occlusion.

Complete arterial occlusion without thrombosis has been reported to occur in various segments of the intracranial circulation, usually peripherally (Ferris and Levine, 1973). Failure to fill the internal carotid artery has been described in cases of raised intracranial pressure and termed "pseudo-occlusion" (Newton and Couch, 1960). This case is exceptional in that it is the first report of non-thrombotic occlusion of the vascular supply to an entire cerebral hemisphere not resulting from increased intracranial pressure.

Pathologic correlation of the left internal carotid demonstrates acute inflammatory cells in the adventitia with only mild intimal thickening. The contralateral cavernous carotid shows changes of focal intimal thickening without inflammatory cellular infiltrations. This appearance is similar to that in early atherosclerosis of the mature circulatory system. The marked angiographic findings are disproportionate to the microscopic structural alterations and this may implicate spasm as a major modifying factor.

REFERENCES

BHANDARI, Y. S., and SARKARI, N. E. S., 1970. Subdural empyema. *Journal of Neurosurgery*, *32*, 35–39.

FERRIS, E. J., and LEVINE, H. L., 1973. Cerebral arteritis: classification. *Radiology*, *109*, 327–341.

FERRIS, E. J., RUDIKOFF, J. C., and SHAPIRO, J. H., 1968. Cerebral angiography of bacterial infection. *Radiology*, *90*, 727–734.

GREITZ, T., 1964. Angiography in tuberculous meningitis. *Acta Radiologica*, (*Diagnostic*) *2*, 369–378.

NEWTON, T. H., and COUCH, R. S. C., 1960. Possible errors in the arteriographic diagnosis of internal carotid artery occusion. *Radiology*, *75*, 766–773.

1978, *British Journal of Radiology*, *51*, 915–916 NOVEMBER 1978

Case reports

Miliary pulmonary infiltrates and penicillamine

By Jørgen Petersen, M.D.,* and Inge Møller, M.D.†

Department of Medicine, Section of Rheumatology and Clinical Immunology,* and Department of Radiology,† University Hospital of Copenhagen, Hvidovre Hospital, DK-2650 Hvidovre, Denmark.

(*Received April, 1978*)

D-penicillamine (D-dimethylcysteine) is used in the treatment of Wilson's disease, cystinuria, scleroderma, and rheumatoid arthritis.

The drug may cause many side effects, including rashes, fever, adenopathy, thrombocytopenia, membranous glomerulonephritis with or without nephrotic syndrome, a disseminated lupus erythematosus-like syndrome, myasthenia gravis, polymyositis-dermatomyositis, and cholestatic jaundice.

Pulmonary complications have also been observed. Sternlieb *et al.* (1975) and McCormick *et al.* (1976) described Goodpasture's syndrome as a side effect. Eastmond (1976) reported a case of diffuse alveolitis induced by penicillamine.

We now report an episode of miliary pulmonary infiltrates in a patient given penicillamine for rheumatoid arthritis.

Diffuse bilateral pulmonary infiltrates following nitrofurantoin therapy have been described by Strauss and Griffin (1967), DeMasi (1967), and Wilson and McCarty (1968). Winterbauer *et al.* (1976) found similar lung changes in two patients following treatment with gold salts. Diffuse bilateral pulmonary infiltrates have been described as complication of methotrexate therapy (Everts *et al.* 1973) and bleomycin therapy (Clinical Screening Co-operative Group of the EORTC, 1970).

CASE REPORT

A 52-year old woman had seropositive, erosive rheumatoid arthritis of four years' duration. She had previously been treated with sodium aurothiosulphate and chloroquine; both drugs were withdrawn because she developed a rash. After two years on prednisone, treatment with penicillamine was started in slowly increasing doses.

After seven weeks of penicillamine therapy at a time when she had received 300 mg a day for seven days and 10 mg prednisone and 1600 mg ibuprofen she developed a generalized skin rash, fever, and non-productive cough.

A chest radiograph revealed miliary infiltrates in both lungs (Fig. 1) which were not present at the time when penicillamine was started. At the same time mild albuminuria, erythrocyturia, and increased levels of alkaline phosphatase and aspartate aminotransferase were observed.

Penicillamine but not ibuprofen or prednisone was discontinued, and the rash and the fever subsided within 48 hours. The pulmonary changes disappeared within two weeks (Fig. 2). Albuminuria and red blood cells in the urine disappeared in two days, and the blood levels of alkaline phosphatase and aspartate aminotransferase returned to normal within three weeks.

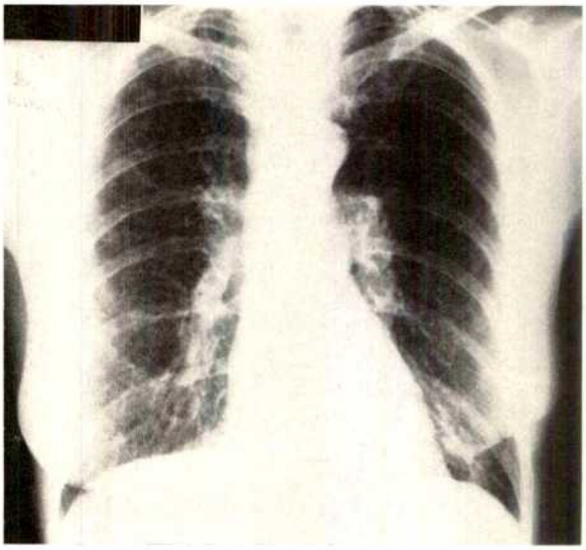


FIG. 1.

A chest radiograph reveals miliary infiltrates in both lungs.

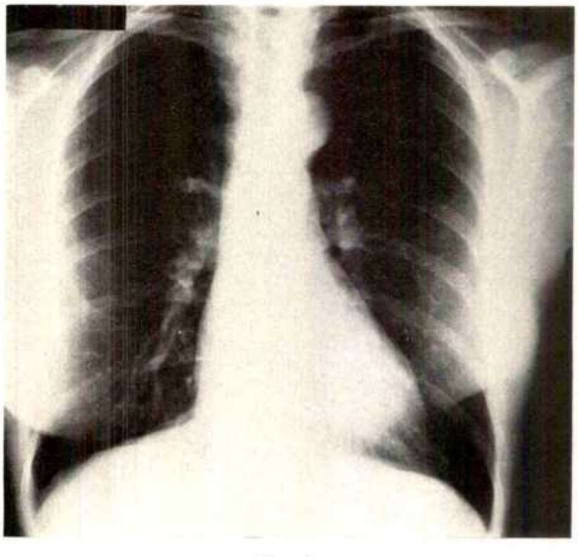


FIG. 2.

Follow-up radiograph (two weeks later) shows complete clearing.

Reprint request to first author at Solkrogen 6, DK–2960 Rungsted Kyst, Denmark.

1978, *British Journal of Radiology*, *51*, 916–917

Laboratory data: Hgb 13.5 g/dl, WBC 11.6×10^9/l with a normal differential count, platelets 295×10^9/l, alkaline phosphatase 1203—252 u/l (50–275 u/l) aspartate aminotransferase 82—15 u/l (10–40 u/l). Urine: protein 0.4 g/l. Sediment: five red cells per h p f.

Cultures from tonsils and pharynx were negative as were several blood cultures. Examination for tubercle bacilli by microscopy and culture was negative.

DISCUSSION

Miliary pulmonary infiltrates have not previously been reported as a complication of treatment with penicillamine.

In our patient penicillamine had been administered for seven weeks before the onset of pulmonary changes which disappeared within two weeks after the drug had been withdrawn. It is unlikely that the lung changes were caused by other drugs given to the patient at the same time, by infection or by the rheumatoid arthritis.

REFERENCES

Clinical Screening Co-operative Group of the EORTC, 1970. Study of the clinical efficiency of bleomycin in human cancer. *British Medical Journal*, *2*, 643–645.

DEMASI, C. J., 1967. Allergic pulmonary infiltrates probably due to nitrofurantoin. *Archives of Internal Medicine*, 120, 631–634.

EASTMOND, C. J., 1976. Diffuse alveolitis as complication of penicillamine treatment for rheumatoid arthritis. *British Medical Journal*, *1*, 1506.

EVERTS, C. S., WESTCOTT, J. L., and BRAGG, D. G , 1973. Methotrextae therapy and pulmonary disease. *Radiology*, *107*, 539–543.

MCCORMICK, J. N., WOOD, P., and BELL, D., 1976. Penicillamine-induced Goodpasture's syndrome. In *Penicillamine Research in Rheumatoid Disease*. Ed. E. Munthe. Proceedings from "Penicillamine in Rheumatic Diseases", Symposium, Norway, March 7th–10th, pp. 268–275.

STERNLIEB, I., BENNETT, B., and SCHEINBERG, I. H., 1975. D-penicillamine induced Goodpasture's syndrome in Wilson's disease. *Annals of Internal Medicine*, *82*, 673–675.

STRAUSS, W. G. and GRIFFIN, L. M., 1967. Nitrofurantoin pneumonia. *The Journal of the American Medical Association*, *199*, 175–176.

WILSON, E. S. and MCCARTY, R. J., 1968. Nitrofurantoin pneumonia. *The American Journal of Roentgenology*, *103*, 540–542.

WINTERBAUER, R. H., WILSKE, K. R., and WHEELIS, R. F., 1976. Diffuse pulmonary injury associated with gold treatment. *The New England Journal of Medicine*, *294*, 919–921.

Bilateral pigmented villonodular synovitis of the hip

By R. L. Eisenberg, M.D., and M. W. Hedgcock, M.D.

Departments of Radiology, University of California School of Medicine, and Veterans Administration Hospital, San Francisco, California 94143, U.S.A.

(*Received December, 1977 and in revised form April, 1978*)

Pigmented villonodular synovitis (PVS) involving the hip joint is unusual; polyarticular involvement is still more unusual. We wish to present a case of bilateral hip joint involvement by PVS.

CASE REPORT

A 42-year-old male was evaluated for progressive right hip pain and joint swelling over a ten-month period. Radiographs revealed marked cystic abnormalities bilaterally involving the acetabulum and the femoral head and neck, both in the immediate subchondral region and at a distance from the joint surface (Fig. 1). The patient also mentioned mild left hip pain, though of far less severity than on the right. Synovectomy of the right hip was performed; the synovial tissue was diffusely thickened with brown nodular proliferations. Pathological examination of the synovium demonstrated numerous villi with haemosiderin-laden polyhedral cells in a mass of connective tissue; the connective tissue was myxoid in some areas and hyaline in others—all these findings were consistent with pigmented villonodular synovitis.

The postsurgical course was uneventful and the patient soon became fully ambulatory. Two years later he began to complain of increasing left hip pain and swelling. Radiographs revealed no change in the bilateral cystic abnormalities. A synovectomy of the left hip was performed and the pathological findings were the same as those for the previously operated side. Again, the postsurgical course was uneventful and the patient became fully ambulatory.

DISCUSSION

Jaffe (1958) stated that pigmented villonodular synovitis involves the knee approximately 10–15 times as frequently as the hip. Only five cases of polyarticular pigmented villonodular synovitis have been reported (Byers *et al.*, 1968; Gehweiler and Wilson, 1969; Greenfield and Wallace, 1950; Leszcynski *et al.*, 1975). Bilateral involvement of the hip by this disease has not previously been reported.

As in most of the previously reported patients having pigmented villonodular synovitis, gradually increasing pain and swelling were the presenting symptoms in our patient. The large cystic areas noted both in the immediate subchondral region and at a distance from the hip joint surface are findings similar to those previously reported (Breimer and Freiberger, 1958; Case Records of the Massachusetts General Hospital, 1944, 1951; Chung and Janes, 1965; Gehweiler and Wilson, 1969; Ghormley and Romness 1954; Jaffe, 1958; McMaster, 1960; Smith and Pugh, 1962). It should be emphasized that such cystic abnormalities occur more in the hip than in

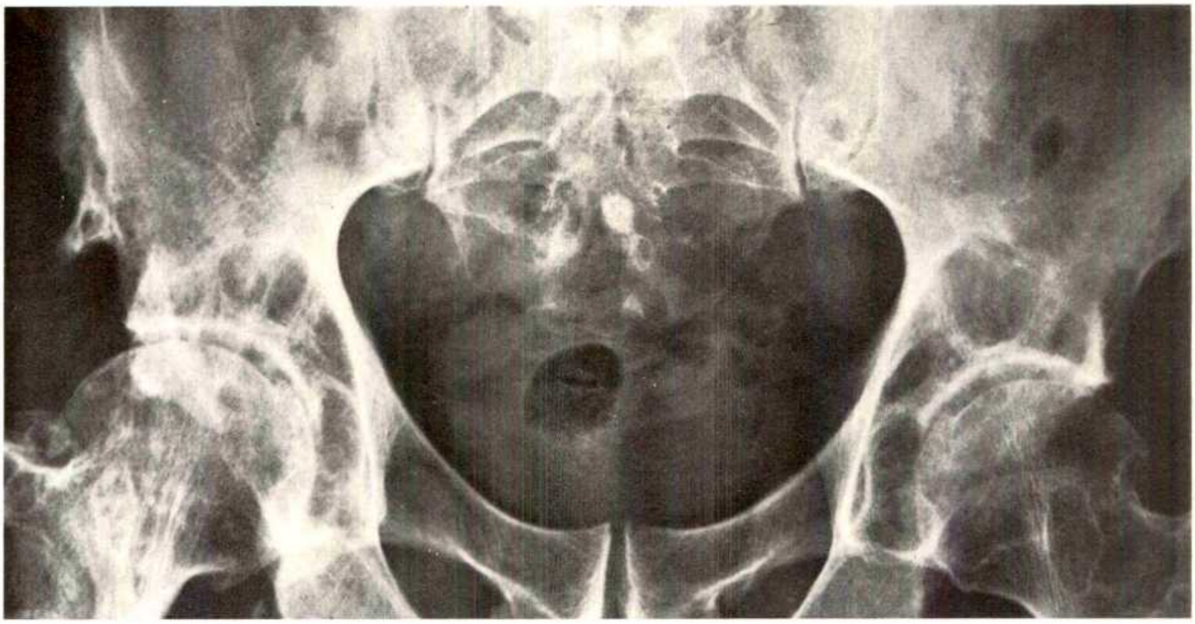


FIG. 1.

Radiograph demonstrates marked cystic abnormalities bilaterally involving the acetabulum and the femoral head and neck.

any other joint (Breimer and Freiberger, 1958). No significant sclerosis of the femoral head was seen in our patient, although this has occasionally been present (Chung and James, 1965; Smith and Pugh, 1962).

Although pigmented villonodular synovitis is usually monoarticular, it should be considered in the differential diagnosis of polyarticular joint disease manifested by joint swelling and cystic abnormalities.

REFERENCES

BREIMER, C. W., and FREIBERGER, R. H., 1958. Bone lesions associated with villonodular synovitis. *American Journal of Roentgenology*, *79*, 618–629.

BYERS, P. D., COTTON, R. E., DEACON, O. W., LOWY, M., NEWMAN, P. H., SISSONS, H. A., and THOMPSON, A. D., 1968. The diagnosis and treatment of pigmented villonodular synovitis. *Journal of Bone and Joint Surgery*, *50-B*, 290–305.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: CASE 30131, 1944. *New England Journal of Medicine*, *230*, 409–412.

CASE 37292, 1951. *New England Journal of Medicine*, *245*, 112–115.

CHUNG, S. M. K., and JANES, J. M., 1965. Diffuse pigmented villonodular synovitis of the hip joint: review of the literature and report of four cases. *Journal of Bone and Joint Surgery*, *47-A*, 293–303.

GEHWEILER, J. A., and WILSON, J. W., 1969. Diffuse biarticular pigmented villonodular synovitis. *Radiology*, *93*, 845–851.

GHORMLEY, R. K., and ROMNESS, J. O., 1954. Pigmented villonodular synovitis (xanthomatosis) of the hip joint. *Mayo Clinic Proceedings*, *29*, 171–180.

GREENFIELD, M. M., and WALLACE, K. M., 1950. Pigmented villonodular synovitis. *Radiology*, *54*, 350–356.

JAFFE, H. L., 1958. *Tumors and Tumorous Conditions of the Bones and Joints*. Philadelphia, Lea and Febiger., P. 534.

LESZCYNSKI, J., HUCKELL, J. R., PERCY, J. S., LERICHE, J. C., and LENTLE, B. C., 1975. Pigmented villonodular synovitis of multiple joints: occurrence in a child with cavernous haemangioma of lip and pulmonary stenosis. *Annals of the Rheumatic Diseases*, *34*, 369–272.

MCMASTER, P. E., 1960. Pigmented villonodular synovitis with invasion of bone: report of six cases. *Journal of Bone and Joint Surgery*, *42-A*, 1170–1183.

SMITH, J. H., and PUGH, D. G., 1962. Roentgenographic aspects of articular pigmented villonodular synovitis. *American Journal of Roentgenology*, *87*, 1146–1156.

1978, *British Journal of Radiology*, *51*, 918

Case reports

Phaeochromocytoma diagnosed during barium meal

By I. Beggs, M.B., M.R.C.G.P.

Department of Diagnostic Radiology, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ

(*Received March, 1978*)

The polypeptide hormone glucagon is used to relax smooth muscle in barium studies of the gastro-intestinal tract. It must be administered with caution in the presence of an insulinoma and is contra-indicated in cases of sensitivity or phaeochromocytoma. I report a case in which glucagon precipitated a hypertensive crisis in a previously unrecognized case of phaeochromocytoma.

CASE REPORT

A 62-year-old woman was referred for a barium meal examination because of a two months' history of nausea, vomiting and epigastric pain. After ingestion of the barium and gas tablets, 1 mg of glucagon hydrochloride was injected intravenously. Within seconds the patient complained of nausea. This rapidly intensified and she began to retch. She was frightened, cold, clammy and shivery. Her blood pressure at five and ten minutes was 300+/170 mm Hg. By 20 min, it was 170/110 mm Hg. After 30 min she still felt very shaken but otherwise well. She received no medication following the glucagon injection.

For months, she had experienced similar episodes, but these were less severe. A provisional diagnosis of phaechromocytoma was confirmed by elevated urine levels of HMMA (hydroxymethoxymandelic acid); elevated catecholamine levels were found in blood sampled from the left renal vein; and angiography demonstrated a left adrenal tumour which was subsequently removed. Histological examination corroborated the diagnosis.

DISCUSSION

Glucagon is frequently administered to relax smooth muscle during barium examinations. It acts from the oesophagus to the rectum and is reputedly more effective than atropinic agents (Kreel, 1975).

A major advantage of glucagon is that it is a relatively safe drug: it is not contra-indicated in glaucoma, prostatism or cardiac failure and it is well tolerated. A dose of 0.25 mg produces satisfactory smooth muscle relaxation without any significant side effects. One of the contra-indications to glucagon is the presence of a phaeochromocytoma. In normal people glucagon releases catecholamines from the adrenal medulla. This may result in a slight elevation of blood pressure. In phaeochromocytomas, which have large quantities of stored catecholamines, the amount released may cause a significant rise of blood pressure and this response has been used as a provocative test. A patient with a definite phaeochromocytoma may not react to intravenous glucagon but a positive pressor response has invariably indicated a phaeochromocytoma (Galloway, 1972). It is theoretically possible that other neural crest tumours might respond similarly.

The typical pressor response (Sheps and Maher, 1968) develops within one minute of injection with a rapid rise of blood pressure. This reaches a peak within five minutes and is over in fifteen minutes. The rise varies from a few millimetres of mercury to the large increase seen in this case. With a large elevation it is advisable to give an intravenous injection of 5 mg of phentolamine mesylate to reduce blood pressure and avoid a vascular catastrophe. Because of this danger, the glucagon provocative test for phaeochromocytomas is not widely used. In the presence of a phaeochromocytoma 0.5 mg of glucagon is usually sufficient to produce a significant blood pressure increase. Surprisingly, this pressor response is often asymptomatic. (Sheps and Maher, 1968). A relatively large dose (1.0 mg) of glucagon precipitated this patient's hypertensive crisis, and the accompanying symptoms allowed the diagnosis to be made. A smaller dose would probably have avoided the danger of a hypertensive crisis although the diagnosis might not have been made because of a paucity of symptoms. 0.25 mg of glucagon produces satisfactory smooth muscle relation (Kreel, 1975). In radiological practice, there seems to be little need to exceed this dose. It is of interest that another commonly used drug in gastro-intestinal radiology, metoclopramide has recently been reported to cause hypertensive crises in cases of phaeochromocytoma (Plouin *et al.*, 1976; Agabiti-Rosei *et al.*, 1977). Glucagon and metoclopramide are useful drugs and should not be abandoned because of their reaction with an uncommon tumour. However, radiologists who administer the drugs should be aware of the hazards and be prepared to deal with them.

REFERENCES

AGABITI-ROSEI, E., ALICANDRI, C. L., and COREA, L., 1977. Hypertensive crisis in patients with phaeochromocytoma given metoclopramide. *Lancet*, *1*, 600.

GALLOWAY, J. A., 1972. The pharmacology and clinical use of glucagon. In *Glucagon, Molecular Physiology, Clinical and Therapeutic Implications*, Edited by P. J. Lefebvre and R. H. Unger, pp. 303–305 (Pergamon Press, London).

KREEL, L., 1975. Pharmaco-radiology in barium examinations with special reference to glucagon. *British Journal of Radiology*, *48*, 691–703.

PLOUIN, P. F., MENARD, J., and CORVOL, P., 1976. Hypertensive crisis in patient with phaeochromocytoma given metoclopramide. *Lancet*, *2*, 1357–1358.

SHEPS, S. G., and MAHER, F. T., 1968. Histamine and glucagon tests in diagnosis of pheochromocytoma. *Journal of the American Medical Association*, *205*, 895–899.

1978, *British Journal of Radiology*, *51*, 919–920

Case reports

A giant retrofemoral Baker's cyst

By K. O. A. Meurman, M.D., A. Luppi, M.D., and M. J. Turunen, M.D.

Department of Radiology and Department of Surgery, First Central Military Hospital, Helsinki, Finland

(*Received January, 1978 and in revised form May, 1978*)

A hundred years ago, in 1877, the Englishman, W. Morrant Baker, published his first report "On the formation of synovial cysts in the leg in connection with disease of the knee-joint". Although other authors before Baker described the same disease, the expression "Baker's cyst" has remained the common term in medical language. Usually the cyst communicates with the joint, either directly or via the bursae in the popliteal fossa (Baker, 1885). The incidence of popliteal cysts in autopsies has been reported to be approximately 50% (Wilson *et al.*, 1938) and the development of arthrography has enlarged our knowledge of the anatomy of these cysts.

The condition is most common in patients with rheumatoid arthritis, osteoarthritis, meniscal tears or with previous effusions in the knee (Burleson *et al.*, 1956; Kirpilä and Ripatti, 1958; Kogstad, 1970; Pallardy *et al.*, 1971). The giant cysts, in particular, are usually found among patients with longstanding rheumatoid arthritis and tend to enlarge downwards into the calf (Harvey and Corcos, 1960; Perri *et al.*, 1968; Taylor, 1969; Barbaric and Young, 1972; Vahvanen, 1973), where the cyst may mimic the clinical picture of deep venous thrombosis (Baker, 1877; Good, 1964; Hench *et al.*, 1966; Haraldsson and Westgren, 1974; Swett *et al.*, 1975). A Baker's cyst has even been reported to cause occlusion of the popliteal artery (Schlenker *et al.*, 1974).

Proximal extension of the cyst is very rare (Reinhardt, 1972). In Pallardy's series (1971) there were five such cases. Grepl (1973) reported two, while Hall and Scott (1966), Hench *et al.* (1966), and Kogstad (1970) each reported one example. All these cysts were confined to the lower femoral region unlike the present example which extended high into the thigh.

CASE REPORT

A previously healthy non-athletic 19-year old male, with no history of knee injury, began his military service. Two weeks later he complained of vague pain in the right knee, and one week later there appeared to be a small effusion present. The joint returned to normal after bed rest for three days but the next strenuous exercise caused recurrence of pain in the joint, this time severe, and associated with pitting oedema of the calf and foot. There was no pyrexia and ESR, Waaler-Rose and Latex tests were normal. The oedema almost completely subsided after four days bed rest but for the first time the patient began to experience pain in the popliteal fossa when climbing stairs. A swelling was noted in the popliteal fossa and a diagnostic puncture produced a clear, yellow viscid fluid similar in nature to that aspirated from the joint. Arthrography revealed a giant, tubular, retrofemoral Baker's cyst measuring 35 × 3 × 2.5 cms. (Fig. 1). At operation, the cyst was tightly adherent to the popliteal artery and vein and to the lower part of the femoral vein, necessitating meticulous excision. The cyst communicated with the knee joint via a narrow neck (Fig. 2) and lay between biceps femoris and semimembranosus muscles with its cranial end deep to gluteus maximus. The cyst, which was synovial in type, contained synovial fluid and fibrinoid material and there was evidence of non-specific infection in its walls.

DISCUSSION

Rheumatoid cysts are often lobulated (Harvey and Corcos, 1960; Hall and Scott, 1966; Perri *et al.*,

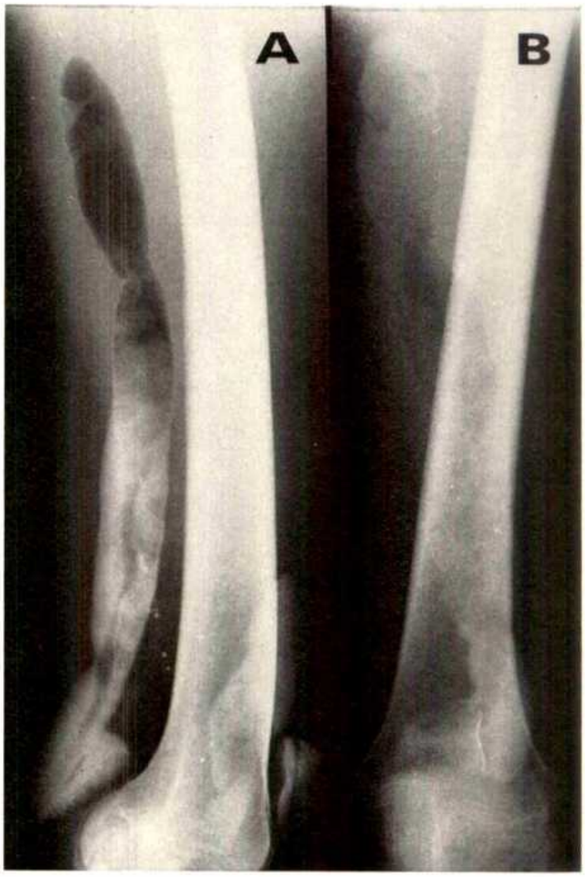


FIG. 1.

A giant tubelike retrofemoral Baker's cyst extended up under the great gluteal muscle.

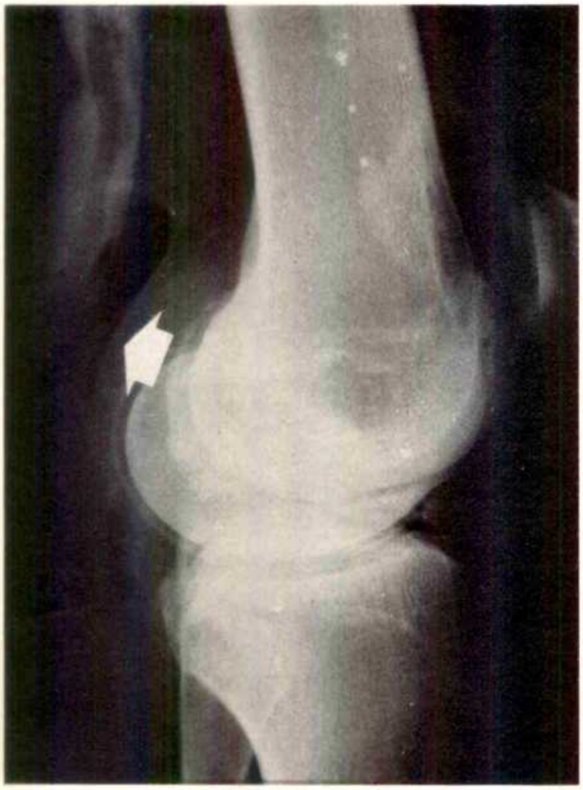


Fig. 2.

A narrow channel connecting the cyst to the knee joint.

1968). Radiographically, the cysts are usually blurred because of fibrinous deposits and villous synovitis (Taylor, 1969; Kogstad, 1970; Barbaric and Young, 1972). In the present case, however, the walls were smooth and the cyst had a regular, tube-like form extending as far as the gluteal region. Serological tests were negative for rheumatoid disease and the patient did not complain of pain in any other joint. Arthrography revealed no evidence of trauma or of osteoarthrosis.

As in this patient, a narrow channel is frequently found connecting the cyst to the joint proper. In these circumstances there is a tendency to a valvular effect of Bunsen type (Jayson and Dixon, 1970) causing synovial fluid to be pumped from the joint into the cyst but not in the reverse direction. The resulting increasing pressure within the cyst contributes to its progressive enlargement. However, this is usually a long-term phenomenon associated with chronic effusion and the great enlargement of this cyst in such a short time is difficult to explain.

The close adherence of the cyst to the popliteal vein together with the mechanical pressure during exercise would explain the clinical impression of deep vein thrombosis; resolution occurred quickly with bed rest because there was, in fact, no intravenous obstruction to blood flow. The aetiology remains obscure.

REFERENCES

Baker, W. M., 1877. On the formation of synovial cysts in the leg in connection with disease of the knee-joint. *St. Bartholomews Hospital Reports*, *13*, 245–261.

1885. The formation of abnormal synovial cysts in connection with the joints. *St. Bartholomews Hospital Reports*, *21*, 177–190.

Barbaric, Z. L., and Young, L. W., 1972. Synovial cysts in juvenile rheumatoid arthritis. *American Journal of Roentgenology*, *116*, 655–660.

Burleson, R. J., Bickel, W. H., and Dahlin, D. C., 1956. Popliteal cyst. A clinicopathological survey. *The Journal of Bone and Joint Surgery*, *38-A*, 1265–1274.

Good, A. E., 1964. Rheumatoid arthritis, Baker's cyst and "thrombophlebitis". *Arthritis and Rheumatism*, 7, 56–64.

Grepl, J., 1973. Beitrag zur positiven Arthrographie bei patologischen Veränderungen der Bursae popliteae. *Fortshcritte aud dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *119*, 84–90.

Hall, A. P., and Scott, J. T., 1966. Synovial cysts and rupture of the knee joint in rheumatoid arthritis. An arthrographic study. *Annals of the Rheumatic Diseases*, *25*, 32–40.

Haraldsson, P.-E., and Westgren, M., 1974. Baker-cysta kan simulera venös trombos. *Svenska Läkartidnigen*, *43*, 4195–4196.

Harvey, Jr., J. P., and Corcos, J., 1960. Large cysts in lower leg originating in the knee occurring patients with rheumatoid arthritis. *Arthritis and Rheumatism*, *3*, 218–228.

Hench, P. K., Reid, R. T., and Reames, P. M., 1966. Dissecting popliteal cyst simulating thrombophlebitis. *Annals of Internal Medicine*, *64*, 1259–1264.

Jayson, M. I. V., and Dixon, A. St. J., 1970. Valvular mechanisms in juxta-articular cysts. *Annals of the Rheumatic Diseases*, *29*, 415–420.

Kirpilä, J., and Ripatti, N., 1958. On Baker's cyst and its treatment. *Acta Rheumatologica Scandinavica*, *4*, 296–302.

Kogstad, O., 1970. Baker's cyste. *Tidskrift för norske Laegeforeningen*, *90*, 488–492.

Pallardy, G., Fabre, P., Ledoux-Lebard, G., Renoux, J.-P., and Debarre, F., 1971. Diagnostic des bursites et kystes poplités par arthrographie du genou. *Revue du Rhumatisme*, *38*, 345–360.

Perri, J. A., Rodnan, G. P., and Mankin, H. J., 1968. Giant synovial cysts of the calf in patients with rheumatoid arthritis. *The Journal of Bone and Joint Surgery*, 50-A, 709–719.

Reinhardt, K., 1972. Popliteacysten und poplitogene Unterschenkelcysten (Baker-Cysten). *Der Radiologe*, *3*, 77–86.

Schlenker, J. D., Johnston, K., and Wolkoff, J. S., 1974. Occlusion of popliteal artery caused by popliteal cysts. *Surgery*, *76*, 833–836.

Swett, H. A., Jaffe, R. B., and Mclff, E. B., 1975. Popliteal cysts: presentation as thrombophelbitis. *Radiology*, *115*, 613–615.

Taylor, A. R., 1969. Arthrography of the knee in rheumatoid arthritis. *The British Journal of Radiology*, 42, 493–497.

Vahvanen, V., 1973. Popliteal cyst. A follow-up study on 42 operatively treated patients. *Acta orthopaedica Scandinavica*, *44*, 303–310.

Wilson, P. D., Eyre-Brook, A. L., and Francis, J. D., 1938. A clinical and anatomical study of the semimembranous bursa in relation to popliteal cyst. *The Journal of Bone and Joint Surgery*, *20*, 963–984.

1978, *British Journal of Radiology*, *51*, 921–922 NOVEMBER 1978

Short communications

Human whole body line-scan imaging by NMR

By P. Mansfield, I. L. Pykett, and P. G. Morris

Department of Physics, University of Nottingham

and R. E. Coupland

Department of Human Morphology, School of Medicine, University of Nottingham

(Received July, 1978)

Historically, the first nuclear magnetic resonance (NMR) pictures demonstrating live human anatomy were produced recently (Mansfield and Maudsley, 1976; 1977) using a line-scanning technique. The original specimens studied were limited in object size to cross-sectional views through fingers. A number of other approaches to imaging by NMR are also being developed and are compared, discussed and referred to elsewhere (Brunner and Ernst, 1978; Pykett and Mansfield, 1978).

Recent development and expansion of our imaging apparatus has now allowed us to examine objects of the dimensions of the whole human body. In this paper we wish to report the first NMR line-scan medical image of a thin cross-sectional slice of a live human body.

Our work should be seen in the general context of other medical imaging schemes (Hounsfield, 1973; Hill, 1976; Budinger, 1974), where improvements in techniques and picture quality have recently achieved very high standards. NMR imaging, however, is in its infancy, but nevertheless has merit as a non-invasive and, we believe, non-hazardous technique. There is also the possibility of using NMR imaging in conjunction with other measurable NMR parameters for normal and abnormal tissue characterization and for physiological studies including blood flow measurements.

Our NMR imaging technique, based on selective excitation in switched magnetic field gradients, was first described by Garroway *et al.* (1974). A slightly modified version of the fast line-scanning adaptation (Mansfield *et al.*, 1976) is the basis of the technique reported in this paper. The thickness of the cross-sectional slice examined was set to approximately four cm in these first experiments. Selected lines of material across the slice are scanned from one edge of the subject to the other and the subsequent data sets for each scanned line are stored in a computer for subsequent display as a picture (Baines and Mansfield, 1976). Large signals which produce the bright zones in the images come in general from high concentrations of mobile protons contained within or near the various tissues and organs. By mobile protons, we have in mind those associated with the free water, fat or oil contained in or distributed throughout the various tissues and organs of the body.

The whole body image shown in Fig. 1 is a transverse section through the abdominal region (of PM) at the level of the third and lower part of the second lumbar vertebrae. Figure 2 is a line tracing of Fig. 1 labelling the recognizable morphological features. The liver is visible as a well-defined mass mainly on the right of the picture and blends with the abdominal wall at the periphery. The vertebrae are identifiable in the mid-line and the kidneys lie in the mid-lateral region with the spleen adjacent on the left. The central circular images probably correspond to the abdominal aorta, with the pancreas lying anterior, inferior vena cava and duodenum. We believe that the variable dense anterior central

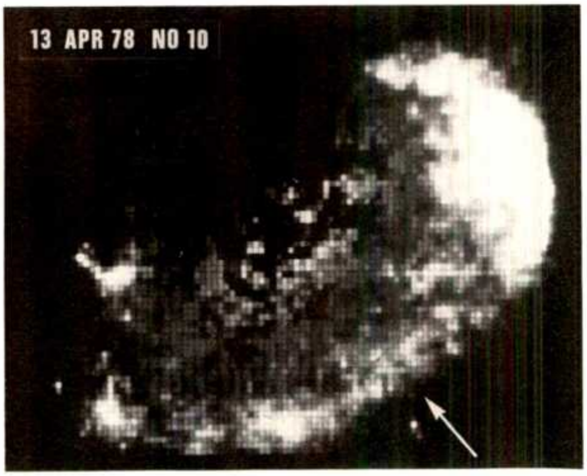


FIG. 1.

Cross-sectional line-scan NMR image through the abdomen at L2-3. Arrow indicates mid-line posterior. Left side lies to the left of the illustration. Bright zones correspond in general to high mobile proton content. See Fig. 2 for labelled details.

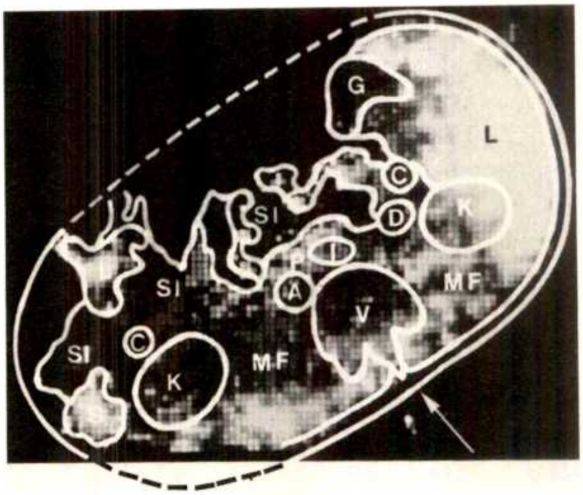


FIG. 2.

Labelled image of Fig. 1. A=aorta, C=colon, D=duodenum, G=gall-bladder, I=inferior vena cava, K=kidneys, L=liver, P=pancreas, S=spleen, SI=stomach and intestines, V=vertebra. Abdominal muscles and retroperitoneal fat (MF) are seen adjacent to the vertebra.

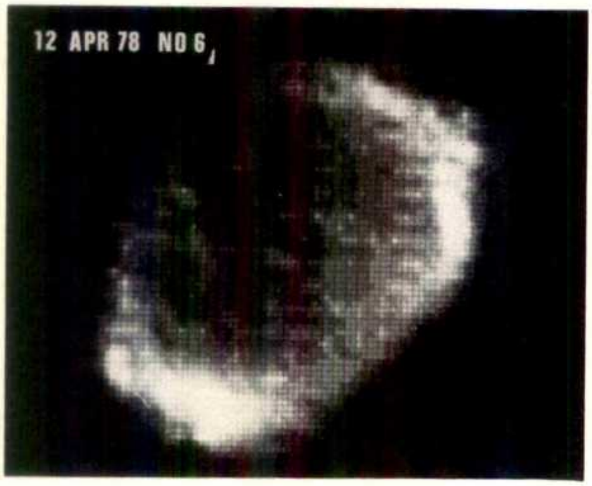


FIG. 3.

Cross-sectional line-scan NMR image through a cadaver thigh. The scan time for this picture was approximately 26 min. The profile of the femur is clearly visible (upper left) with central bone marrow.

region shows parts of the stomach and intestines and profiles of colon are anterior to the kidneys. The ovoid outline anteriorly and to the right, associated with the liver image, is probably gall-bladder.

The image of Fig. 1 comprises 75 × 90 picture elements and took 40 min. to produce. Each line of the picture was averaged 96 times. Some loss of picture quality is ascribed both to involuntary bodily movements, especially respiration, and lack of complete r.f. penetration at 4.0 MHz, the NMR resonance frequency used in these experiments. Some correction for the latter effect and some data enhancement has been applied in Fig. 1. The effect of movement could be minimized by using ultra high-speed planar NMR imaging techniques (Mansfield and Pykett, 1978).

A cadaver thigh section image shown in Fig. 3 reveals the femur, femoral vessels and profunda femoris vessels and other morphological detail using raw data only. The extra clarity reflects the importance of restricting movement.

Magnetic field gradients of approximately 0.04 G cm^{-1} were used and passed through the whole of the torso region. Switching the gradients in 50 μsec produced no sensations whatsoever. As an initial precaution live rabbits, rats and guinea pigs were previously subjected to switched gradients and a cat was scanned with no problems a day before the human experiments.

The first whole-body line-scan experiment was performed during the evening of April 13, 1978 and has produced no acute or chronic ill-effects to date.

The electromagnet used for this work was built by Oxford Instruments and comprises four air-cored concentric coils approximating to a spherical magnet design. Dispersed iron used in the construction of the physics research building impairs the static performance of the magnet and causes some non-linearity and degradation of the spatial resolution of our first whole-body pictures.

Our experiments were performed at a repetition frequency of 3 Hz. As a general caveat we suggest that frequencies in the range 30–150 Hz, known to be dangerous in a.c. electric shock, should be avoided in any future experiments. Similar precautions should also be taken to avoid known alpha-wave brain frequencies if head scanning experiments are planned.

ACKNOWLEDGMENTS

We are grateful to the MRC for support of the whole body NMR imaging project, the SRC for some staff support, D. Kerr and R. Ordidge for their assistance in the design and construction of some of the apparatus, and D. Whelpton and R. Potter for use of and assistance with the computing facilities of the Medical Physics Department.

We are especially indebted to T. Baines for the design and construction of the electronic apparatus and V. Bangert for his assistance in the design of the gradient coils.

REFERENCES

BAINES, T., and MANSFIELD, P., 1976. An improved picture display for NMR imaging. *Journal of Physics, E, 9*, 81–83.

BRUNNER, P., and ERNST, R. R., 1978. Sensitivity and performance time in NMR imaging. *Journal of Magnetic Resonance* (in press).

BUDINGER, T. F., 1974. *Recent Advances in Nuclear Medicine*, ch. 2, ed. J. H. Lawrence (Grune and Stratton, New York).

GARROWAY, A. N., GRANNEL, P. K., and MANSFIELD, P., 1974. Image formation in NMR by a selective irradiative process. *Journal of Physics, C, 7*, L 457–461.

HILL, C. R., 1976. Ultrasonic imaging. *Journal of Physics, E, 9*, 153–162.

HOUNSFIELD, G. N., 1973. Computerized transverse axial scanning (tomography). *British Journal of Radiology, 46*, 1016–1022.

MANSFIELD, P., and MAUDSLEY, A. A., 1976. Planar and line-scan imaging by NMR, Proc. 19th Congress Ampere, Heidelberg (Gronpeinent Ampere, Heidelberg, Geneva) 247–252.

1977. Medical imaging by NMR. *British Journal of Radiology, 50*, 188–194.

MANSFIELD, P., MAUDSLEY, A. A., and BAINES, T., 1976. Fast scan proton density imaging by NMR. *Journal of Physics, E, 9*, 271–278.

MANSFIELD, P., and PYKETT, I. L., 1978. Biological and medical imaging by NMR. *Journal of Magnetic Resonance, 29*, 355–373.

PYKETT, I. L., and MANSFIELD, P., 1978. A line scan study of a tumorous rat leg by NMR. *Physics in Medicine and Biology 23*, 961–967.

1978, *British Journal of Radiology*, *51*, 923–924 NOVEMBER 1978

Short communications

Radiation response of mice maintained on a defined diet

By Shirley Lehnert, Ph.D.*

University Surgical Clinic, Montreal General Hospital, Montreal, Quebec, Canada

(*Received April, 1978*)

The use of a defined diet consisting of readily absorbable nutrients ("elemental diet") has been reported to protect the intestinal epithelium of rats against lesions associated with 5-fluorouracil (Bounous *et al.*, 1971*a*) and to increase 30-day survival in mice following 900 rad of X rays (Hugon and Bounous 1972). A diet of this type has been used in the management of patients with intestinal lesions induced by 5-fluorouracil (Bounous *et al.*, 1971*b*) and other anti-tumour agents (Cousineau *et al.*, 1973) and has been administered to patients undergoing a course of radiotherapy for tumours of the abdominal region (Bounous *et al.*, 1973).

The effect of ingestion of a defined diet on the response of mice to whole body irradiation has been investigated in this laboratory. Mice maintained on the defined diet (diet-fed) were allowed unlimited access to Meade Johnson Product 3200-A.S. (Table I) in powdered form from seven days prior to irradiation until the end of the experimental period. They were observed to gain weight at the same rate as their control counterparts who were fed Purina mouse chow *ad libitum* (chow-fed).

Table II shows the mean lethal dose (MLD) of X rays at seven days and 30 days post-irradiation for chow-fed and diet-fed mice. Clearly post-irradiation survival is unchanged in mice maintained on the defined diet. This observation is at variance with the findings of Hugon and Bounous (1972) who showed enhanced survival for diet-fed mice at 30 days post-irradiation.

Survival curves for clonogenic cells of the intestinal crypts are shown in Fig. 1. The exponential slopes of the

TABLE I

COMPOSITION OF THE DEFINED DIET

Components	g.%
Mead Johnson casein hydrolysate*	24.9
Sucrose	44.7
Mead Johnson medium-chain triglycerides*	6.9
Corn oil	4.3
Olive oil	10.4
Cod liver oil	1.3
Vitamin mixture†	2.5
Salt mixture (Hegsted)	5.0

*Mead Johnson Company of Canada Ltd., Belleville, Ontario.
†Vitamin diet fortification mixture, Nutritional Biochemical Corporation, Cleveland, Ohio.

TABLE II

MEAN LETHAL DOSE (RAD) AT 7 AND 30 DAYS

	Mean Lethal Dose ± S.E.	
	7 Days	30 Days
Control	1186±13.0 (1160–1212)*	575±8.0 (559–591)
Fed defined diet 7 days prior to irradiation	1180±11.0 (1158–1202)	560±9.0 (542–578)

*95% Confidence limits of Mean Lethal Dose.

Swiss ICR/HAM male mice (weight 25.0±2.0 gm.) were irradiated with 225 kV, 15 mA X rays (FSD 37.5 cm, dose rate 54 rad/minute). Approximately 120 mice were irradiated in the appropriate dose range, and MLD was calculated from the survival curve by the probit method.

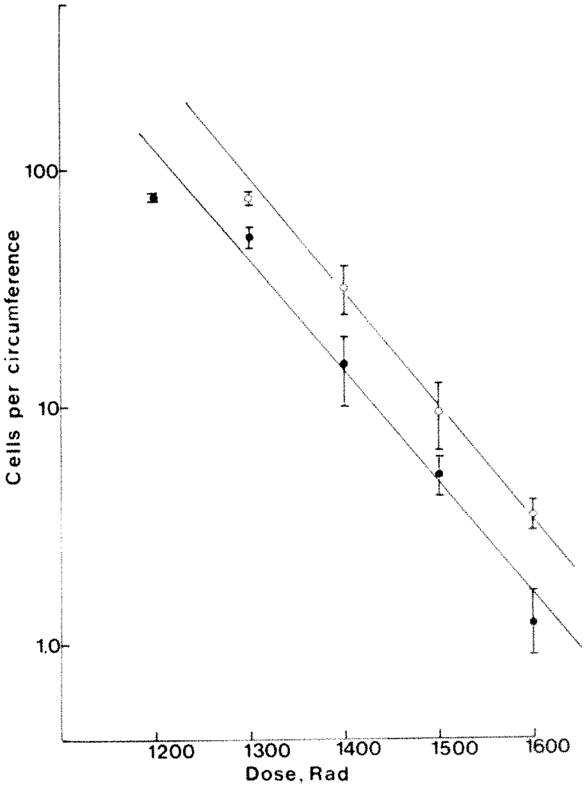


FIG. 1.

Survival curves for crypt stem cells from chow-fed (o—o) or diet-fed mice (●—●) mice. Animals were killed approximately three and a half days after irradiation and the number of viable crypts per circumference was counted on cross-sections of the jejunum. The number of cells surviving a given dose or irradiation was calculated by correcting for crypts regenerating from more than one surviving cell according to Poisson statistics (Withers and Elkind, 1970).

---

*Present address: Department of Therapeutic Radiology, Royal Victoria Hospital, 687 Pine Avenue W., Montreal H3A 1A1, Quebec, Canada.

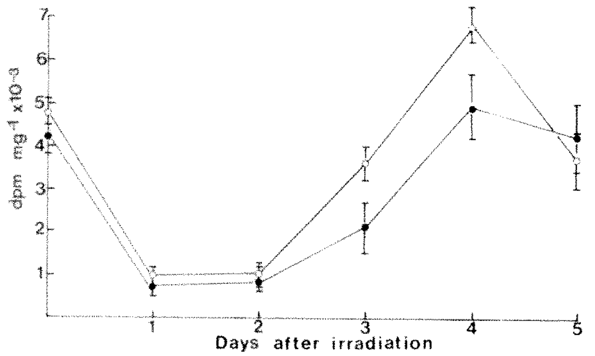


FIG. 2.

Incorporation of tritiated thymidine into the jejunum of mice at various times after 1100R whole body irradiation. Six mice were sacrificed in each group. Vertical bars represent standard error. (○—○) chow-fed mice (●—●) diet-fed mice. 50 μCi ^{3}H-Thymidine (specific activity 2.0 Ci/mM, New England Nuclear) was injected intraperitoneally 60 minutes prior to sacrifice. Radioactivity was assayed in a weighed solubilized portion of jejunum by liquid scintillation counting.

curves for control or diet-fed mice are the same at all dose levels studied, although the survival of crypt stem cells in chow-fed mice was approximately twice that found in diet-fed mice. The fact that if extrapolated back to zero dose the curve for diet-fed mice would cut the abcissa at a lower point than that for control mice suggests that the number of clonogenic cells in the non-irradiated crypt is lower in diet-fed mice than in chow-fed mice.

In another experiment, the post-irradiation proliferative capacity of the gut was studied in chow-fed and diet-fed mice. Following a dose of 1100R whole body radiation, incorporation of tritiated thymidine into the jejunum fell to a minimum within one day of irradiation, remained low for the following day and then increased reaching a maximum at four days after irradiation (Fig. 2). At this time, the rate of incorporation exceeded that seen prior to radiation and this overshoot reflects the occurrence of the high level of compensatory proliferation which repopulates the intestinal epithelium following sub-lethal doses of radiation. The same pattern was observed in both diet-fed and chow-fed mice, but in diet-fed animals the initiation of the increase in incorporation of tritiated thymidine following irradiation was delayed by approximately 16 hours and the compensatory overshoot in proliferative activity observed in control was not seen.

The results of the two experiments just described suggest that feeding of the defined diet to mice prior to irradiation has produced changes in the growth kinetics of the intestinal epithelium with the result that the number of proliferative cells in the crypt is reduced at the time of irradiation and post-irradiation proliferation is delayed and reduced in extent.

In summary, the results of the investigations described here indicate that feeding of the defined diet to mice before irradiation has no radioprotective effect in terms of mortality and that the ability of the animal to regenerate intestinal epithelium rapidly following irradiation is slightly impaired, possibly as a result of changes in intestinal cell kinetics induced during the pre-irradiation feeding period.

ACKNOWLEDGMENTS

These investigations were supported by the John A. Hartford Foundation. I am indebted to Claudette Labelle and Kathy Key for technical assistance.

REFERENCES

BOUNOUS, G., HUGON, J. and GENTILE, J. M., 1971a. Elemental diet in the management of lesions produced by 5-fluorouracil in rats. *Canadian Journal of Surgery, 14*, 298–311.

BOUNOUS, G., GENTILE, J. M., and HUGON, J., 1971b. Elemental diet in the management of intestinal lesions produced by 5-fluorouracil in man. *Canadian Journal of Surgery, 14*, 312–324.

BOUNOUS, G., TAHAN, W., SHUSTER, J., GOLD, P., COUSINEAU, L., ROCHAN, M and LEBEL E. 1973. The use of an elemental diet during abdominal radiation. *Clinical Research, 21*, 1066.

COUSINEAU L., BOUNOUS, G., ROCHON, M., SHUSTER J., GOLD P. and TAHAN W., 1973. The use of an elemental diet during treatment with anticancer agents. *Clinical Research, 21*, 1066.

HUGON, J. S. and BOUNOUS G., 1972. Elemental diet in the management of the intestinal lesions produced by radiation in the mouse. *Canadian Journal of Surgery, 15*, 18–25.

WITHERS, H. R. and ELKIND, M. M., 1970. Microcolony survival assay for cells of mouse intestinal mucosa exposed to radiation. *International Journal of Radiation Biology, 17*, 261–267.

1978, *British Journal of Radiology*, *51*, 925 NOVEMBER 1978

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Repression of the medical profession in Argentina

THE EDITOR—SIR,

The choice of Argentina by the International Union Against Cancer (IUAC) for the forthcoming 12th International Cancer Congress in October raises an important ethical question, since there is a great deal of evidence to show that political repression, arrest without trial, and the systematic use of torture have become extremely common in Argentina, and doctors, together with members of allied professions, have been prominent among the victims.

Information received by Amnesty International (AI) indicates that since the military coup of March 24, 1976 some 15000 persons have disappeared after being arrested, and a further 8000 are known to be political prisoners. Doctors have been specially vulnerable, and while it is possible that some have been involved in guerilla organizations AI has good evidence to show that many have been arrested on flimsy pretexts or none at all. Currently some 80 members of the medical or affiliated professions are known to have disappeared; many others have had to flee the country or have been dismissed from their posts. Some of those arrested have been brutally tortured and others have been killed. (AI can supply detailed evidence to anyone interested.)

Individual doctors in other countries may well feel that they would like to make some kind of protest about the situation in Argentina in the context of the IUAC congress. But what steps should they take? Should they, for example, boycott the congress?

Some have, in fact, decided to do so. The French newspaper *Le Monde* has published a statement by 291 French doctors who have refused to attend a congress held in Buenos Aires, and a similar statement has been signed by between 400 and 500 American doctors. However, it is possible to argue against the effectiveness of boycotts: for example, it could be said that to maintain contact with the rest of the world would be valuable for the morale of Argentinian doctors. Clearly this is something that each doctor must decide for himself or herself; AI is *not* asking for a boycott, but only seeking to bring the facts to the notice of the medical profession in general and of doctors attending the congress in particular.

Whether one attended the congress or not, it is open to one to make a protest about the violation of human rights that is occurring in Argentina. AI suggests the following measures:

1. Write *in your professional capacity* to the Argentinian President and Minister for Social Security, whose addresses are: Su Excelencia Jorge Rafael Videla, Presidente de la República Argentina, Casa Rosada, Buenos Aires, Argentina. Excelentísimo Señor Ministro Almirante Julio Juan Bardi, Ministro de Bienestar Social, Ministerio de Bienestar Social, Defensa 12, Buenos Aires, Argentina.
2. Write to the president of the National Organizing Committee of the 12th International Congress, expressing your solidarity with members of the medical profession who are suffering repression and protesting at their mistreatment: A. N. Canónico, c/o XII International Cancer Congress, Casillo de Correo 397, Correo Central 1000, Buenos Aires, Argentina.
3. Write to the Secretary General of the IUAC, Gerald Murphy, asking him and his organization to make enquiries about colleagues who have disappeared or been arrested in Argentina.

In addition, doctors who attended the Congress can talk to colleagues about the problem, and they could consider taking additional steps such as calling a special press conference.

Anyone who wants to know more about the tragic situation in Argentina should contact Amnesty International, British Section, Tower House, 8–14 Southampton Street, London WC2E 7HF.

Yours, etc.,
ANTHONY CAMPBELL.

2 Bishopswood Road,
Highgate,
London N6 4PR.

Radiation exposure to the patient in computerized tomography

THE EDITOR—SIR,

As part of the evaluation tests performed on the EMI CT5005 whole-body scanner installed at the Royal Marsden Hospital, Surrey, measurements have been made to estimate the maximum exposure to the skin of the patient. The Mark II scanner used has a redesigned collimator which differs from the prototype machine for which exposure measurements have been reported previously (Rutherford *et al.*, 1976).

The CT5005 whole-body scanner operates by translate-rotate motion, involving a rotation of 180 deg. in 10 deg. steps. Scanning times of 20 sec and 70 sec are available. Three sizes of image reconstruction can be carried out, 24 cm, 32 cm and 40 cm, each with a fixed slice width of 13 mm. The 24 cm reconstruction is used for skulls and small children with an operating voltage of 120 kVp, and the 32 and 40 cm reconstructions are used for adult body scanning at 140 kVp. The existing algorithms on the EMI scanner are designed for use with circular cross-sections which are approximated in practice by the use of bolus bags. The bolus consists of polystyrene spheres coated with latex, suspended in talcum powder and encased in a latex envelope, each piece being 1.5 cm thick. As the use of bolus is undesirable in some situations, exposures have been measured with and without the bolus bags in position.

A Temex skull phantom, measuring 15 × 14 cm in cross-section, with bone and air cavities (Cat. No. B, James Girdler & Co. Ltd.) was used for simulating the head. For body scanning, a Temex trunk phantom measuring 29 × 19.5 cm in cross-section was used.

The exposures were measured using TLD dosimeters in the form of LiF chips measuring 3 mm × 3 mm × 0.8 mm. These were calibrated against an ionization chamber

TABLE I

MAXIMUM EXPOSURE TO THE SURFACE OF A TEMEX SKULL PHANTOM. 24 CM RECONSTRUCTION: 120 kV NORMAL (20 SEC) SCAN SPEED

Slice interval	Without bolus		With bolus	
	1 slice	8 slices	1 slice	8 slices
1.0 cm	4.6 R	7.1 R	3.5 R	6.0 R
1.3 cm	4.6 R	5.6 R	3.5 R	5.1 R
1.5 cm	4.6 R	5.0 R	3.5 R	4.8 R

1978, *British Journal of Radiology*, *51*, 926–927

TABLE II

MAXIMUM EXPOSURE TO THE SURFACE OF A TEMEX TRUNK PHANTOM. 32 CM AND 40 CM RECONSTRUCTION 140 KV. NORMAL (20 SEC) SCAN SPEED

Slice interval	32 cm reconstruction				40 cm reconstruction			
	Without bolus		With bolus		Without bolus		With bolus	
	1 slice	8 slices	1 slice	8 slices	1 slice	8 slices	1 slice	8 slices
1.0 cm	2.3 R	4.6 R	1.8 R	3.6 R	2.8 R	5.9 R	2.2 R	4.2 R
1.3 cm	2.3 R	3.5 R	1.8 R	3.1 R	2.8 R	4.5 R	2.2 R	3.6 R
1.5 cm	2.3 R	3.0 R	1.8 R	2.9 R	2.8 R	4.0 R	2.2 R	3.4 R

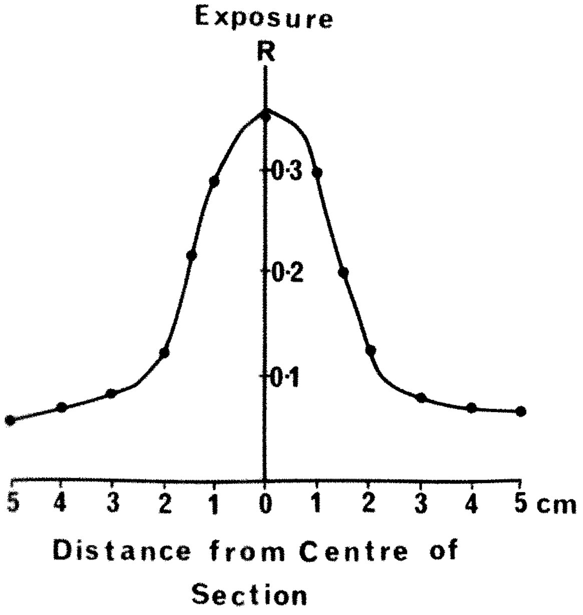


FIG. 1.

Exposure along the mid-line longitudinal axis of a Temex trunk phantom for a single scan. Normal scan speed; 32 cm reconstruction.

(Nuclear Enterprises type 2561) with 150 kVp X rays produced by an X-ray generator similar to that in the whole body scanner. The position of maximum exposure was found by placing dosimeters around the circumference of the scanned slice at 1 cm intervals over a 200 deg arc.

Since most CT examinations consist of scanning several contiguous slices, the exposure to a single slice will be increased due to scatter from its neighbours. Surface exposures to the phantom in the direction perpendicular to the plane of the scan were therefore investigated for a single scan, and using this information the exposure to the surface for multiple scans was calculated for various distances between slices (*i.e.* slice intervals). For some cases these calculations were checked by scanning eight contiguous slices on the Temex phantom; the two methods agreed to within ±2%.

Tables I and II show the maximum exposures recorded for the three reconstruction sizes, for scanning with and without bolus and for single and multiple slices, using the normal (20 sec) scanning speed. For the slow (70 sec) scan speed the exposure will increase by a factor of 3.6.

Figure 1 shows the measured exposure as a function of distance along the mid-line axis in the centre of the Temex trunk phantom, with one piece of bolus placed on the anterior surface. Measurements using LiF chips were recorded for a single normal scan at 140 kVp for a reconstruction size of 32 cm. These results were used to calculate the exposure to the mid-line for multiple slices, and values of 1.2, 1.0 and 0.9 R were obtained for slice intervals of 1 cm, 1.3 cm and 1.5 cm respectively.

In practice most patients have between 12 and 15 contiguous body slices scanned, at an interval of 1.5 cm using the normal scanning speed and bolus. The skin exposure under these conditions is estimated from these measurements as 3.2 R. However, for brain scanning most patients have eight contiguous slices at 1.5 cm intervals, and many of these examinations are repeated with contrast media. For 20 sec scans an exposure of 9.6 R is received. It follows that if the slow 70 sec scan speed were used, with and without contrast media, the maximum exposure would be as high as 36 R. For slices near the orbit, the lens may well receive exposures of this magnitude.

Yours, etc.,
PAULINE HOBDAY,
R. P. PARKER.

Physics Department,
Royal Marsden Hospital and
Institute of Cancer Research,
Downs Road,
Sutton,
Surrey SM2 5PT.

REFERENCES

RUTHERFORD, R. A., PULLAN, B. R., and ISHERWOOD, I., 1976. The physical performance of a prototype CT5005 EMI body scanner. In *Proceedings of the 1st European Seminar on Computerised Axial Tomography in Clinical Practice*, eds G. H. Du Boulay and I. F. Moseley, pp. 301–311 (Springer-Verlag, Berlin, Heidelberg, New York).

The effect of misonidazole on lymphocytes

The Editor—SIR,

Misonidazole (Ro 07-0582) is a radiosensitizer of hypoxic cells (Denekamp and Harris, 1975). Early studies with radiotherapy patients have been encouraging (Thomlinson *et al.*, 1976). However, peak plasma levels of 100 μg/ml in patients have been associated with neurotoxicity (Dische *et al.*, 1977). Since the drug is cytotoxic (Moore *et al.*, 1976; Josephy *et al.*, 1978) its effect has been tested on human lymphocytes *in vitro*, to gain insight into other side effects that might occur in clinical practice. The endpoints measured have been suppression of phytohaemagglutinin (PHA) stimulated transformation and mitosis, production of chromosomal and chromatid exchanges and breaks, and the

TABLE I

Misonidazole (μg/ml)	Transformation index (%)	Mitotic index (%)	Chromosome breaks per cell	Chromatid breaks per cell	SCE per chromosome
0	95.4 ± 4.1	1.4 ± 0.5	0.03 ± 0.02	0	0.09 ± 0.01
31.25	81.1 ± 3.9	2.3 ± 0.7	0	0	0.13 ± 0.02
62.5	81.5 ± 3.8	2.1 ± 0.7	0.03 ± 0.02	0.01 ± 0.01	0.17 ± 0.02
125.0	74.1 ± 3.6	2.4 ± 0.7	0.05 ± 0.02	0.03 ± 0.02	0.14 ± 0.01
250.0	77.5 ± 3.6	0.2 ± 0.2	0.11 ± 0.05	0	0.14 ± 0.04
500.0	68.5 ± 3.6	0	0.04 ± 0.02	0.01 ± 0.01	—

induction of sister chromatid exchanges (SCEs). The concentrations of misonidazole used (donated by Roche Products Ltd.) were based on plasma levels determined in patients, where a concentration of up to 415 μg/ml has been achieved (Gray *et al.*, 1976). Lymphocyte culture and harvesting techniques were carried out under aerobic conditions and were similar to those reported by Moorhead *et al.* (1960), except that each culture contained the drug and 10 μm 5-bromodeoxyuridine and was maintained in the dark throughout. Cells were harvested at 74 h. in a dark-room illuminated through an Ilford S902 filter. Cell preparations were either stained with Giemsa alone, or first with Hoechst 33258, exposed to ultraviolet light, and then stained with Giemsa to detect SCEs (Latt, 1973; Wolff and Perry, 1974). For each dose of drug used, 500 cells were scored to determine the transformation and mitotic index, 100 cells in metaphase for chromosome damage and 300 chromosomes for SCE. The results (± 1 SE) are shown in Table I. The number of chromosome or chromatid breaks per cell was derived by multiplying the number of observed exchanges by two and adding to this the number of fragments detected (Lea and Catcheside, 1942).

The untreated lymphocytes responsed to PHA normally, except that three acentric fragments were detected. At the largest dose of drug, 500 μg/ml, there was a significant reduction ($p < 0.05$) in transformation with an associated reduction in mitotic index. These effects are at levels well above the plasma concentrations of 20 μg/ml which are planned for phase two clinical trials (Dische *et al.*, 1977). There was no significant increase in the amount of chromosome or chromatid damage or SCEs at any dose, suggesting that misonidazole may not exhibit significant long term lymphocytoxicity if these cells are well oxygenated *in vivo*. However, this will require confirmation using the blood of radiotherapy patients undergoing treatment with the drug.

Yours, etc.,
M. G. CLARE,
C. A. JOSLIN.

Department of Radiotherapy,
University of Leeds,
Regional Radiotherapy Centre,
Cookridge Hospital,
Leeds LS16 6QB.

REFERENCES

DENEKAMP, J., and HARRIS, S., 1975. Tests of two electron affinic radiosensitizers *in vivo* using regrowth of an experimental carcinoma. *Radiation Research*, *61*, 191–203.

DISCHE, S., SAUNDERS, M. I., LEE, M. E., ADAMS, G. E., and FLOCKHART, I. R., 1977. Clinical testing of the radiosensitiser Ro-07-0582: experience with multiple doses, *British Journal of Cancer*, *35*, 567–579.

GRAY, A. J., DISCHE, S., ADAMS, G. E., FLOCKHART, I. R., and FOSTER, J. L., 1976. Clinical testing of the radiosensitiser Ro-07-0582. I. Dose tolerance, serum and tumour concentration. *Clinical Radiology*, *27*, 151–157.

JOSEPHY, P. D., PALCIC, B., and SKARSGARD, L. D., 1978. Ascorbate enhanced cytotoxicity of misonidazole. *Nature*, *271*, 370–372.

LATT, S. A., 1973. Microfluorometric detection of deoxyribonucleic acid replication in human metaphase chromosomes. *Proceedings of the National Academy of Science, USA*, *70*, 3395–3399.

LEA, D. E., and CATCHESIDE, D. G., 1942. The mechanism of the induction by radiation of chromosome aberrations in Tradescantia. *Journal of Genetics*, *44*, 216–245.

MOORHEAD, P. S., NOWELL, P. C., MELLMAN, W. J., BATTIPS, D. M., and HUNGERFORD, D. A., 1960. Chromosome preparations of leukocytes cultured from human peripheral blood. *Experimental Cell Research*, *20*, 613–616.

MOORE, B. A., PALCIC, B., and SKARSGARD, L. D., 1976. Radiosensitizing and toxic effects of the 2-nitroimidazole Ro-07-0582 in hypoxic mammalian cells. *Radiation Research*, *67*, 459–473.

THOMLINSON, R. H., DISCHE, S., GRAY, A. J., and ERRINGTON, L. M., 1976. Clinical testing of the radiosensitiser Ro-07-0582. III. Response of tumours. *Clinical Radiology*, *27*, 167–174.

WOLFF, S., and PERRY, P., 1974. Differential Giemsa staining of sister chromatids and the study of sister chromatid exchanges without autoradiography. *Chromosoma (Berl.)*, *48*, 341–353.

Care with radiosensitizers

The Editor—SIR,

In current radiotherapy trials with the oxygen-mimetic radiosensitizing drugs, which are expected to overcome the potential problem of resistant hypoxic tumour cells, no allowance is being made for sensitization of normal tissue. These new agents are competing with hyperbaric oxygen (HBO) for providing therapeutic benefit, and sensitization by HBO was observed in the skin (van den Brenk *et al.*, 1965), in laryngeal cartilage (Churchill-Davidson, 1968; Henk *et al.*, 1977) and in the neuraxis (Coy and Dolman, 1971). Subsequently, a 10% reduction in dose was estimated as necessary with those HBO treatments of advanced head and neck cancer where laryngeal cartilage was irradiated (Henk and Smith, 1977). Even higher reductions are suggested from experimental findings using rodents (Table I)—the mean is 35% from 11 experiments.

Misonidazole causes a smaller enhancement of radiation damage in normal tissue than HBO (about half, Table I). Nevertheless, we suggest that a reduction in radiation dose of at least 5% should still be considered when using misonidazole with irradiation volumes which include cartilage. Some groups investigating the clinical use of misonidazole may use radiation doses below "tolerance", such that any dose-enhancing effect of misonidazole, resulting in more-severe late damage to normal tissue, could be obscured. However, if doses of high NSD are used, a small "effective" increase in dose may increase unacceptably the incidence of late complications, due to the steepness of the dose-response curve (Morrison, 1975; Stewart and Jackson,

TABLE I

SENSITIZATION OF NORMAL TISSUE IN RODENTS

Hyperbaric oxygen > 1 atmosphere			Misonidazole 1 mg/g		
System	DEF*	Reference	System	DEF*	Reference
Tail stunting	1.3	Howard-Flanders and Wright (1957)	Leg skin	1.0–1.3	Brown (1974)
Leg skin	1.6	van den Brenk *et al.* (1962)	Thigh skin	1.1	Yuhas *et al.* (1977)
Leg skin	1.2–1.5	Withers and Scott (1964)	Foot skin	1.2	
Leg skin	1.6–2.2	Fowler *et al.* (1965)	Hair loss	1.0	
Tail stunting	1.2	Dixon (1967)	$LD_{50/30}$	0.9	
Skin clones	1.2	Withers (1967)	Testis	1.3	Suzuki *et al.* (1977)
Leg skin	1.6	Suit and Howard (1967)	Tibial cartilage	1.3	Gonzales and Breur (1978)
Brain weight	1–2	Hopewell and Wright (1969)	Tail necrosis	1.1–1.5	Hendry (1978)
$LD_{50/30}$	1.1	Christensen *et al.* (1969)			
$LD_{50/5}$	1.1				
Intestine	1.0	Sigdestad *et al.* (1973)			
Mean = 1.35			Mean = 1.16		

*Dose Enhancement Factor, expressed as the ratio of the dose in air to that in the modified condition to produce equal effect.

1975). Failure to recognize this potential hazard could seriously prejudice any success of this and other similar agents.

Yours, etc.,
J. H. HENDRY,
M. L. SUTTON.

Christie Hospital and Holt Radium Institute,
Manchester M20 9BX.

REFERENCES

BROWN, J. M., 1974. Selective radiosensitization of the hypoxic cells of mouse tumours with the nitroimidazoles, metronidazole and Ro 07-0582. *Radiation Research*, *64*, 633–647.

CHRISTENSEN, G. M., DAHLKE, L. W., GRIFFIN, J. T., MOUTVIC, J. C., and JACKSON, K. L., 1969. The effect of high-pressure oxygen on acute radiation mortality in mice. *Radiation Research*, *37*, 283–286.

CHURCHILL-DAVIDSON, I., 1968. Long-term effects of hyperbaric oxygen and irradiation on non-neoplastic tissues. In *Frontiers of Radiation Therapy and Oncology*, *1*, pp. 134–140 (Karger, Basel/New York).

COY, P., and DOLMAN, C. L., 1971. Radiation myelopathy in relation to oxygen level. *British Journal of Radiology*, *44*, 705–707.

DIXON, B., 1967. The effect of radiation on the growth of vertebrae in the tails of rats. I. Single doses of X rays and the effect of oxygen. *International Journal of Radiation Biology*, *13*, 355–368.

FOWLER, J. F., KRAGT, K., ELLIS, R. E., LINDOP, P. J., and BERRY, R. J., 1965. The effect of divided doses of 15 MeV electrons on the skin response of mice. *International Journal of Radiation Biology*, *9*, 241–252.

GONZALES, D. G., and BREUR, K., 1978. Dose-modifying effect of misonidazole on the radiation response of growing cartilage in mice. *British Journal of Cancer*, *37*, Suppl. III, 235–236.

HENDRY, J. H., 1978. Radionecrosis of normal tissue: studies on mouse tails. *International Journal of Radiation Biology*, *33*, 47–55.

HENK, J. M., KUNKLER, P. B., and SMITH, C. W., 1977. Radiotherapy and hyperbaric oxygen in head and neck cancer. Final report of the first controlled clinical trial. *Lancet*, *ii*, 101–103.

HENK, J. M., and SMITH, C. W., 1977. Radiotherapy and hyperbaric oxygen in head and neck cancer. *Lancet*, *ii*, 104–105.

HOPEWELL, J. W., and WRIGHT, E. A., 1969. A demonstration of the oxygen effect in irradiated brain. *International Journal of Radiation Biology*, *16*, 593–596.

HOWARD-FLANDERS, P., and WRIGHT, E. A., 1957. The effect of oxygen on the radiosensitivity of growing bone in the tail of the mouse. *British Journal of Radiology*, *30*, 593–599.

MORRISON, R., 1975. The results of treatment of cancer of the bladder—a clinical contributon to radiobiology. *Clinical Radiology*, *26*, 67–75.

SIGDESTAD, C. P., HAGEMANN, R. F., and SCOTT, R. M., 1973. The effect of oxygen on intestinal crypt survival in cobalt-60 irradiated mice. *Radiation Research*, *54*, 102–109.

STEWART, J. G., and JACKSON, A. W., 1975. The steepness of the dose response curve both for tumour cure and normal tissue injury. *The Laryngoscope*, *85*, 1107–1111.

SUIT, H. D., and HOWARD, T. C., 1967. Normal tissue damage and tumour cure probability for irradiation given under different conditions of tissue oxygenation in hybrid mice. *Radiology*, *89*, 720–726.

SUZUKI, N., WITHERS, H. R., and HUNTER, N., 1977. Radiosensitization of mouse spermatogenic stem cells by Ro-07-0582. *Radiation Research*, *69*, 598–601.

VAN DEN BRENK, H. A. S., ELLIOTT, K., and HUTCHINGS, H., 1962. Effect of single and fractionated doses of X rays on radiocurability of solid Ehrlich tumour and tissue reactions *in vivo*, for different oxygen tensions. *British Journal of Cancer*, *16*, 518–534.

VAN DEN BRENK, H. A. S., KERR, R. C., RICHTER, W. R., and PAPWORTH, M. P., 1965. Enhancement of radiosensitivity of skin of patients by high pressure oxygen. *British Journal of Radiology*, *38*, 857–864.

WITHERS, H. R., and SCOTT, O. C. A., 1964. The oxygen effect in normal tissues. *British Journal of Radiology*, *37*, 720.

WITHERS, H. R., 1967. The effect of oxygen and anaesthesia on radiosensitivity *in vivo* of epithelial cells of mouse skin. *British Journal of Radiology*, *40*, 335–343.

YUHAS, J. M., YURCONIC, M., KLIGERMAN, M. M., WEST, G., and PETERSON, D. F., 1977. Combined use of radioprotective and radiosensitizing drugs in experimental radiotherapy. *Radiation Research*, *70*, 433–443.

Correspondence

Design of tomographic equipment

THE EDITOR—SIR,

The paper on multi-directional tomographic units (Phelps and Ashley, 1978) prompts me to mention a related problem in the design of tomographic equipment.

Inclined frontal tomography of the chest (Greenwell and Wright, 1965), is a useful technique which produces tomographic sections parallel to the long axis of organs lying at an angle to the sagittal or coronal planes. The essential mechanical requirement is the ability to tilt the X-ray cassette parallel to the plane to be tomographed.

Most X-ray departments do not possess and cannot easily justify purchasing, tomographic units that provide other than simple linear movement, yet it is in just these departments, and the hospital and clinics they serve, that the practical value of inclined-plane tomography would be appreciated.

I have tried, without success, to interest manufacturers in the development of a modified cassette-tray in which the cassette can be tilted at a pre-determined angle to the table-top. Although their usual (and commercially understandable) response is to try to interest one in a more sophisticated machine, this does not seem to be a case in which one has to buy a Rolls-Royce to ensure that the clock keeps good time, since apart from the Polytome the facility does not exist at all.

Cannot some manufacturer be persuaded to develop and market such a simple accessory and so enable any department possessing a linear tomograph to produce inclined plane tomograms at small extra cost?

Yours, ets.,
F. P. GREENWELL.

X-ray Department,
St. Mary Abbots Hospital,
Marloes Road,
Kensington W8 5LQ.

REFERENCES

GREENWELL, F. P. and WRIGHT, F. W., 1965. Rotational tomography. *Clinical Radiology 16*, 377–389.

PHELPS, P. D. and ASHLEY, A. J., 1978. A comparitive survey of multi-directional tomographic units. *British Journal of Radiology*, *51*, 437–442

SI units

THE EDITOR—SIR,

The letter from P. S. Iyer (1978) indirectly draws attention to what seems to be a defect of SI nomenclature, namely the dogma that units must bear the names of eminent persons. For this reason we have lost the self-evident reciprocal ohm (mho) and such a practical proposal as the get will undoubtedly founder on the same reef, along with my own proposal, made elsewhere, for the "gyem" (grey equivalent man) instead of Sievert. Doubtless we shall soon find speed limits expressed in benz (m.sec^{-1}).

Yours, etc.,
G. E. SMYTHE.

M.E.L.
Manor Royal,
Crawley,
West Sussex, RH10 2PZ.

REFERENCE

IYER, P. S., 1978. NSD, CRE, TDF and SI units. *British Journal of Radiology*, *51*, 473.

Maintenance of "Graf Pen"

THE EDITOR—SIR,

A number of radiotherapy centres use "Graf Pen" digitizers for entering isodose curves, patient contours, and other anatomical data into their computers. Some users have experienced a deterioration in performance of the digitizer, and this is due generally to an aging process in the microphone ribbons. For repair or replacement, the manufacturers in the USA recommend that all faulty equipment be returned to them, at considerable cost. However, work carried out at this establishment indicates that a much less costly, yet satisfactory, restoration of performance may be obtained in a short time.

The capacitor microphones are of the electret type. These, briefly, are parallel plate capacitors in which one plate is the aluminized surface of a Mylar ribbon having a "built-in" electric field. The ribbon is of thickness 125 gauge, and the metallized surface is earthed. The other plate is rigid and provides the signal connection to the input of the pre-amplifier. During manufacture each ribbon has been heated almost to its melting temperature and allowed to cool in the presence of an electric field which causes a static charge to remain on it. This charge enables the microphones to function without the need for the external biassing which is required by other types of capacitor microphone. However, after relatively long periods, *i.e.* two years or more, the charge slowly diminishes, and this results in a deterioration of performance.

One approach to the problem is to isolate the Mylar ribbons from the chassis, and, at the ends away from the right-angle joint (for convenience) to connect a permanent biassing voltage of around 100 V d.c. between the ribbon and chassis.

Alternatively (and more elegantly), the charge on the ribbon may be restored by simulating the manufacturing process. Again, an external bias is required, but in this case only temporarily. It should, however, be greater, at around 400 V, as only a small percentage of the field is retained after heating. Connection may be as described above so a word on isolation of the ribbon may be helpful. At the end where the microphones are joined this may be achieved by carefully cutting through the ribbons and removing the short excess lengths clamped around the microphone bases. Some double-sided adhesive will hold the ends in place. At the other ends the clamps must be removed and insulating plates of Perspex fixed under the ribbon. The sockets facilitate connection of the bias supply and, afterwards, reconnection of the ribbon to the chassis via a short lead attached under one of the existing cover screws. Figure 1 shows our arrangement.

Instead of the need for isolation in this manner, it is possible to remove the wire link from the rigid plate at the input of the pre-amplifier and attach to the rigid plate the positive pole of the biassing voltage. The negative connection is to the chassis. Where microphones are made up as multiples of the basic twelve inch length, all sections must be similarly isolated and connected together.

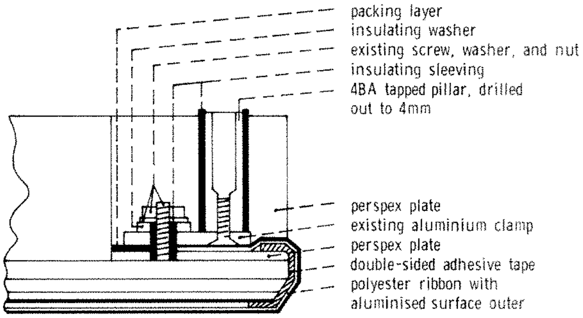

packing layer
insulating washer
existing screw, washer, and nut
insulating sleeving
4BA tapped pillar, drilled out to 4mm
perspex plate
existing aluminium clamp
perspex plate
double-sided adhesive tape
polyester ribbon with aluminised surface outer

FIG. 1.
Insulating assembly.

We found that use of a hot-air blower was suitable in obtaining the required heating, care being taken to avoid localized overheating which results in the ribbon curling up!

One of our ribbons was damaged by handling: the aluminized surface is extremely thin and should not be touched, particularly where the ribbon wraps round the end of the microphone arm because this is the place where the electrical continuity of the surface is most easily destroyed. We have replaced a complete ribbon by using a carefully opened polyester capacitor of value 1μF. It contained more than enough ribbon wound up inside it but a capacitor with sufficient working voltage (more than 400 V) must be chosen. This source provided ribbon of the required width and with a suitable non-aluminized strip along the edge. We obtained equal success in biassing this ribbon and the original ribbons.

Obviously, none of this work should be attempted while the equipment is still under guarantee.

Yours, etc.,
R. J. WILLETTS.

Instrumentation Section, Department of Medical Physics,
Royal Postgraduate Medical School,
Du Cane Road,
London, W12 OHS.

Medical iconography

THE EDITOR—SIR,

Proposal: Medical iconography is proposed as a name to include all body imaging techniques.

There is a need for a good term to indicate the whole group of "body-imaging" techniques, which is universally acceptable in all types of languages. We suggest the term "medical iconography".

Iconography is derived from the Greek ikonos = image, picture and later: painting and graphein = write.

Medical iconography has many advantages:

1. It covers very well the dual function of radiologists, sonographists, etc., *e.g.* the fact that "images" are "written" and/or "described" (*i.e.* making and reading of pictures).
2. Confusion could only exist with "art sciences" where iconography means the description of paintings, or because it is associated with iconoclast, which in fact is the reverse.
3. It is a clear word in all types of languages (Helleno-Latin, German, Slavic, medical, general).
4. It is historical. With the coming of normal photography in the beginning of this century in Paris, a magazine was founded by J. M. Charcot in the Salpêtrière and this was called: *Iconographie médicale et artistique* (Masson et Cie, 1913).
5. Medical iconography can include all types of imaging: thermography and radiography; normal and infrared photography; ultrasound or sonography; CT-scan; nuclear imaging techniques; electroradiography and ENSCAN T. M.; nuclear magnetic resonance and other new imaging techniques.
6. This term emphasizes the unity of all these techniques and the fact that they should be concentrated in one department. The people performing these techniques should all have the same basic roots in anatomy, pathology and perception of "diagnostic images".
7. The name iconology could indicate this science (of perception) itself. The name of the scientists: iconologist? (or iconoloog, iconologue, iconolog).
8. One could even already foresee the "foreshortening" of medical iconography to "ike" *e.g.* Med-ikes (or Ikons); Therm-ikes; Rad-ikes; Sone-ikes, etc., and then in plural we see the X, now preceded by "Ay" turning up again; Med-ixe; Therm-ixe; Sone-ixe.

Yours, etc.,
C. B. A. J. PUIJLAERT.

Department of Radiodiagnosis,
University Hospital,
Catharijnesingel 101,
Utrecht, The Netherlands.

The design of the detector and collimators of a hybrid scanner

THE EDITOR—SIR,

We have read with great interest the article in the November issue of this Journal, (Vauramo and Virjo, 1977). In agreement with the authors we believe the hybrid scanner to have some advantages especially in whole body scintigraphy. Therefore we are developing a prototype and are now testing it.

We have measured the attenuation of scintillation-light in dependence on the point of origin of the scintillations. The attenuation is not exponential along the whole crystal, as might be expected, particularly at both ends. This is due to the characteristics of reflection by the reflector and crystal, and to the attenuation of a broad beam. We have therefore chosen another mode of signal processing, illustrated in Fig. 1. This mode is much simpler: the linearization stage enables each monotonically decreasing function to be fitted by an adequate choice of the operating points of equalizers. Since the calibration may be altered by means of push buttons, the peak height of all pulses can be made equal for all the nuclides of interest. By this mode of operation we have achieved good linearity. Pulse evaluation is now reduced to establishing the difference (localization) and the sum (energy) of both pulses.

Yours, etc.,
H. PROPP.

Radiologische Klinik der
Wilhelm-Pieck-Universität,
Gertrudenplatz,,
25 Rostock, D.D.R.

REFERENCE

VAURAMO, E., and VIRGO, A., 1977. The design of the detectors and collimators for a hybrid scanner. *British Journal of Radiology*, *50*, 808–813.

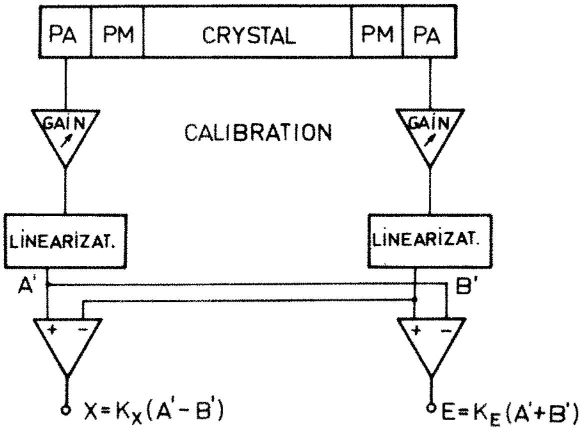


Fig. 1.

Simplified block diagram of signal processing in our prototype hybrid scanner.

Correspondence

The design of the detector and collimators of a hybrid scanner

(*In reply*)

The Editor—Sir,

We have read the comment of Mr. H. Propp (1978). In later measurements our group has noticed a similar deviation from the exponential attenuation law, especially at both ends of the crystal. If a correction is not made for this nonlinearity, it will cause distortion in the picture. We feel that Mr. H. Propp's solution is a good way to eliminate the effect. On the other hand the deviation from an exponential law does not make our statistical estimation of accuracy invalid, as the estimation procedure can be readily modified for any arbitrary attenuation law.

Yours, etc.,
E. Vauramo,
A. Virjo.

Department of Medical Physics,
Central Hospital of Tampere,
SF-33520 Tampere 52,
Finland.

REFERENCE

Propp, H., 1978. The design of the detector and collimators of a hvbrid scanner. *British Journal of Radiology*, *51*, 930.

ICRP 1977 recommendations and handling of radionuclide generators

The Editor—Sir,

The problem of high doses to the finger tips in the handling of ^{113}In^{m} and ^{99}Tc^{m} generators and during injection of the radiopharmaceuticals into the patient has been of concern to the health physicist over the last decade. One naturally turns to ICRP for guidance on dose limits.

Paragraphs 182 and 183 of the latest ICRP recommendations (ICRP, 1977) deal with skin monitoring. It is mentioned that for external radiation there is not likely to be any problem of averaging and that a representative dosimeter reading could be related to the dose-equivalent limit; for surface contamination of the skin, notably the hands, the irradiation will not be uniform and for routine purposes it is adequate to regard the contamination as averaged over 100 cm^2 and the limit applied to the dose-equivalent so averaged. In the case of accidents or suspected accidents it is recommended that an estimate be made of the average dose-equivalent over 1 cm^2 in the region of the highest dose equivalent and this value compared with the dose-equivalent limit.

Now in the case of handling of generators, the problem is external irradiation and not contamination, and not an accident but part of normal operations. However the dose distribution will be extremely non-uniform and there is no question of a representative dosimeter reading being adequate in the sense used in para 182. In this case are we to average over 100 cm^2 or 1 cm^2? If the averaging is over 1 cm^2, the non-stochastic annual dose limit of 50 rem will severely restrict the scope of work with generators. Incidentally this non-stochastic limit is less than the 75 rem allowed by the earlier recommendation to hands and forearms (ICRP, 1966).

The report of the task group on "Radiosensitivity and spatial distribution of dose" (ICRP, 1969) has something relevant to say on this point. After a discussion of the radiobiological aspects, paragraph 34 says that "when small areas of skin are irradiated, the Task Group recommends that the present limit of 30 rem in a year, averaged over 1 cm^2 of skin, be increased to at least 100 rem in a year, with the proviso that irradiation of the same area year after year should be avoided if possible". Of course the proviso cannot be adhered to in the present instance unless a right-handed person could be persuaded to become periodically left-handed. The Task Group report led one to expect that the latest ICRP recommendation would give a categorical ruling on finger doses, keeping in view the urgency of the problem of protection while handling radionuclide generators.

Yours etc.,
A. Nagaratnam,
A. R. Reddy.

Institute of Nuclear Medicine &
Allied Sciences,
Probyn Road,
Delhi—110007, India.

REFERENCES

ICRP, 1966. Recommendations of the International Commission on Radiological Protection (adopted September 17, 1965), ICRP Publication 9, Pergamon Press.

1969. Radiosensitivity and Spatial Distribution of Dose, Reports prepared by two task groups of Committee 1., ICRP Publication 14, Pergamon Press.

ICRP, 1977. Recommendations of the International Commission on Radiological Protection (adopted January 17, 1977) ICRP Publication 26, Pergamon Press.

The discovery of X rays

The Editor—Sir,

The interpretation placed by E. Fischmann (Fischmann, 1978) on alterations contained in Wilhelm Conrad Röntgen's original manuscript, "A New Kind of Rays", is indeed convincing in so far as it seeks to establish historical authenticity. Moreover, Sir James Mackenzie Davidson in his account of a discussion with Röntgen held not long after the discovery of X rays, recalled that Röntgen referred specifically to the use of a Hittorf tube (Kaye, 1914).

However, it would be unfortunate if this point caused the significance of Lenard's own work to be underestimated. At the suggestion of Hertz, Lenard constructed an ingenious form of vacuum tube, equipped with a thin aluminium window which allowed the cathode rays to be transmitted outside the tube. It was Lenard's systematic study of these "emergent cathode rays", or "Lenard rays" as they were then described, that subsequently enabled Röntgen to recognize the "X rays".

The suggestion that the contribution of Lenard (Freund, 1946), or of other researchers of electricity in high vacua such as Varley, Hittorf, Crookes, and Hertz, be accorded greater recognition does not detract from Röntgen's achievements. In his paper entitled "A New Kind of Rays" (Röntgen, 1896), first published after seven weeks of intensive research, Röntgen not only described the absorption properties of X rays and their ability to produce fluorescence in a variety of materials, but also established that X rays do not obey the laws of optics, are not deviated by magnetic forces, and that the X rays originate wherever the cathode rays strike the wall of the vacuum tube. Röntgen even anticipated X ray diffraction by suggesting that "the geometrical arrangement of the molecules might affect the action of a body upon the X rays".

The scientific significance of Röntgen's discoveries was placed in perspective as early as March 1896 when Sir James Dewar remarked ". . . Of course they (critics of Röntgen) always felt that somebody else might have discovered something and that it was a pity he missed it; but really one man could not monopolise everything, and there was plenty yet to be found out".

Yours etc.,
C. B. Smith.

Department of Clinical Physics and
Bio-Engineering,
11 West Graham Street,
Glasgow G4 9LF.

REFERENCES

Fischmann, E., 1978. Alterations in the manuscript of Röntgen's publication "Ueber eine neue Art von Strahlen" (1895), *British Journal of Radiology*, *51*, 475–476.

Freund, F., 1946. Lenard's share in the discovery of X rays, *British Journal of Radiology*, *19*, 131–132.

Kaye, G. W. C., 1914. In *X-rays: An Introduction to the study of Röntgen rays*, Longmans, Green & Co., London, Appendix I.

Röntgen, W. C., 1896. A new kind of rays, *Nature*, *53*, 274–277.

Obituary

Francis Richard Berridge, M.A., M.B., B.Chir., F.R.C.P., F.R.C.R., F.F.R.R.C.S.I., D.M.R.

Dr. Francis Richard Berridge died suddenly on April 19 when about to go dinghy sailing with one of his grandchildren near his home at Wells-next-the-Sea in Norfolk. He was 67. He was formerly consultant radiologist to the United Cambridge Hospitals and to Newmarket General Hospital.

Dick Berridge entered Trinity College, Cambridge, as a Pensioner from Downside School in 1928 and obtained his B.A. in 1930. He went on to do his clinical training at St. George's Hospital and took the Conjoint Diploma in 1934. He proceeded to the Cambridge B.Chir. in 1936 and in the same year passed with distinction the University of London Diploma in Medical Radiology. In the following year he took the Cambridge M.B., and was awarded the Cambridge M.A. in 1938.

Soon after he obtained the Diploma in Radiology he was appointed resident radiologist to the Oldchurch Hospital, Romford, where he stayed for two years before being invited to become assistant in research in radiology to Professor J. A. Ryle, the Regius Professor of Physics at Cambridge University.

Until his retirement 38 years later, diagnostic radiology in Cambridge and Dick Berridge were synonymous. When the war broke out in 1939 he was debarred from military service by his deafness which was already severe but served as specialist radiologist in the Emergency Medical Service at Addenbrooke's Hospital and at what was to become Newmarket General Hospital. At the end of the war in 1945 his special interest and experience in radiology of the gastro-intestinal tract was recognized by an invitation to join Professor R. A. McCance's Medical Research Council unit in Germany to study under-nutrition in liberated Europe. He was appointed associate lecturer in radiology at Cambridge University in 1948 and became a Fellow of the Faculty of Radiologists in 1951 following the submission of his thesis on "The Small Intestine in Under-nutrition". He was honorary medical editor of The British Journal of Radiology from 1956 to 1961, a task which he performed with enthusiasm and distinction. He was elected to the Membership in 1961 and to the Fellowship of The Royal College of Physicians in 1968. He was awarded the Barclay Medal of the British Institute of Radiology in 1963 for his internationally recognized contributions to gastrointestinal radiology. His distinction as a diagnostic radiologist and his Irish connections were acknowledged by the Faculty of Radiologists of The Royal College of Surgeons of Ireland in 1974 by the award of a Fellowship, an honour which afforded him great pleasure.

Although he had a wide knowledge of diagnostic radiology and maintained a broad interest throughout his career, he made gastroenterology his special subject. His early interest in skeletal radiology was sustained by his long and close association with Mr. E. S. Jamieson, his orthopaedic colleague at Newmarket General Hospital. He had an impressive list of publications extending from 1939 to 1978, mainly but not exclusively related to gastrointestinal radiology. Not only was he an excellent diagnostician but he was greatly interested in technical developments in electro-mechanical engineering and cine-radiography. In collaboration with the late Mr. A. F. Jeans of Philips he designed and developed the Cambridge table, a remote control screening unit especially suitable for gastrointestinal investigations.

Dick Berridge was a demanding, stimulating and delightful colleague. His stature as a clinician and radiologist, together with his foresight and tenacity of purpose achieved much for diagnostic radiology in Cambridge. Beginning his consultant career at Addenbrooke's Hospital in a three-roomed department he was, before his retirement, to head one of the largest and most up-to-date departments in a provincial teaching hospital in this country. It was no accident that the University accepted that an Academic Department of Radiology had an important part to play in the newly-created School of Clinical Medicine in Cambridge. Dick's vision of the future and his advocacy of the role of radiology in teaching and in research won the support of those members of the University with open minds and he had the satisfaction of seeing the establishment of a Chair in Radiology and the appointment of the first Professor.

Dick was a man of such energy that his retirement two years ago took many by surprise. He was a constant source of new ideas and although many were visions before their time, there was much to stimulate those privileged to work closely with him. Despite his intellectual stature, he was in many ways a shy and humble man, who genuinely sought the views of his colleagues and accepted their opinions without reserve. Although he was not active in formal lecturing, perhaps due to his shyness, his great contribution to teaching was through the small clinico-radiological meeting, at which he excelled. The breadth and depth of his knowledge was apparent to all and his incisive questions kept his clinical and radiological colleague on their toes. It was not possible to sit down with Dick for five minutes without learning something from him, be the subject clinical radiology, the art of fly-fishing or small boat sailing. He knew and loved Connemara well, where he spent his childhood and he had a deep interest in and knowledge of Yeats' poetry and the Irish literary movement of the early part of this century.

Dick together with his wife Virginia were ideal hosts and one always accepted an invitation from them with pleasurable anticipation. A visit to them on an idyllic summer's day at their lovely home in Norfolk and which gave hope for a long and tranquil retirement, remains a treasured memory. Alas, it was not to be, but the way of Dick's going was how he would have wished it. Virginia, so great a strength and comfort to him, Hugh his son, Priscilla, Mary and Celia his daughters, and their children, must miss him sorely, as do those who had the privilege to be friends and colleagues of this remarkable man.

Desmond Hawkins.

1978, *British Journal of Radiology*, *51*, 933–940 NOVEMBER 1978

Proceedings of The British Institute of Radiology

Recent advances in hyperthermia research

Abstracts of papers presented at a Radiobiology Work-in-Progress meeting held in The Reid-Knox Hall, British Institute of Radiology, 32 Welbeck Street, London W1, on May 11–12, 1978

Technical aspects of applying hyperthermia
Thermometry and water-bath heating, by J. E. Robinson.
Measurement of the electrical properties of materials of biological interest, by R. J. Sheppard.
Recent developments in microwave heating, by J. W. Hand.
A technique for producing localized measurable hyperthermia in superficial rat tumours using radio-frequency currents, by P. B. Dunscombe and B. M. Backhouse.
Heat transfer and conduction in radio-frequency heating, by R. Strang and J. Patterson.
Ultrasonic hyperthermia: a feasibility study, by G. R. ter Haar.
Athermal effects of microwaves at the cellular level, by N. W. Ramsey.
Biological aspects of hyperthermia
The response to combined hyperthermia and radiation of an experimental mammary carcinoma and its surrounding normal tissue, by J. Overgaard.
Thermal enhancement ratio and therapeutic gain in seven experimental mouse tumours, by Sally A. Hill, Fiona Stewart and Juliana Denekamp.
Combined X rays and hyperthermia: loss of therapeutic advantage with fractionation, by Fiona A. Stewart and Juliana Denekamp.
Increase in differential radiosensitivity between two Chinese hamster cell lines after hyperthermic pretreatment, by H. Schlag and Christine Lucke-Hühle.
Metastases and immunological studies in C_3H mice after hyperthermia, by A. S. Abdelaal, Susan M. Chamberlain, A. H. W. Nias and Agnes Walker.
Some effects of heat on red blood-cell morphology, by W. T. Coakley, L. A. Crum, J. O. T. Deeley and A. J. Bater.
The influence of combined hyperthermia and gamma irradiation on different *in vivo* cell populations, by H.-J. Weber, W. Porschen, L. E. Feinendegen and F. Dietzel.
In vivo assay of the radiation sensitivity of euoxic and hypoxic tumour cells; influence of γ-rays, cyclotron neutrons, hyperthermia and mixed modalities, by W. Porschen, H.-J. Weber, H. Muhlensiepen and L. E. Feinendegen.
Single or fractionated hyperthermic treatment of malignant and normal tissue, by J. Overgaard and H. D. Suit.
The role of glucose infusion in hyperthermia, by M. von Ardenne.
A study of thermal damage by time lapse cinemicrography, by Helen Bass, J. L. Moore, W. T. Coakley and L. A. Crum.
The interaction of radiation and hyperthermia in an eukaryotic microbial model system, by J. Kiefer.
The influence of pH on the enhancement of radiation damage by hyperthermia, by J. Lunec and R. Parker.
The response of cancer cells to hyperthermia at low pH, by J. A. Dickson.
The effects of hyperthermia on lysosomal enzyme activity in solid tumours and in cultured cells, by G. M. Barratt, M. Keech and E. D. Wills.
Thermal tolerance *in vivo*, by Marilyn P. Law.
Thermal tolerance and drug cytotoxicity *in vitro*, by J. E. Morgan, D. J. Honess and N. M. Bleehen.
Two qualitatively different effects of hyperthermia on lysosomal enzyme activity in mouse spleen, by S. P. Hume, M. A. Rogers and S. B. Field.

Reprints of these abstracts are available free on application to the Managing Editor, BRITISH JOURNAL OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG (01–935 6867).

THERMOMETRY AND WATER-BATH HEATING

By J. E. Robinson

MRC Cyclotron Unit,
Hammersmith Hospital,
Du Cane Road, London W12 OHS

This paper reviews basic aspects of thermometry, describes some special purpose thermometers, and discusses physical and biological aspects of water-bath heating. The most commonly used thermometers in hyperthermia are mercury-in-glass (used as laboratory sub-standards), thermistors and thermocouples, of which the last two can be inserted directly into tissues. Good practice requires frequent intercomparison and maintenence of a sub-standard traceable to a national standards laboratory. Thermometry problems in electromagnetic fields have resulted in the development of non-metallic probes and special high resistance thermistor devices to reduce measurement artifacts. Using commercially available temperature controllers it is not difficult to obtain temperature uniformity over the central region of water baths to within 0.01°C. Thermal uniformity of biological test objects depends very much upon the region and volume heated. A mouse mammary tumour implanted on the flank and heated by immersion was uniform to within 0.05°C. The same size tumour implanted on the leg showed significant regions with temperatures 1.5°C or more below that of the water bath. The exteriorized mouse gut heated by water bath had regions near mesenteric blood vessels which heated slower and reached equilibrium temperatures lower than regions away from the vessels. Temperatures near the vessels were as much as 2°C lower and rates of heating were as much as three times slower than those far from the vessels. Analysis of crypt counts (Hume, S. P., personal communication) suggests that a temperature difference of about 1.5–2.0°C would be required to account for the differential cell kill observed near to and far from the mesentery, in agreement with the temperature measurements. Assessment of the distance over which the gradient of biological damage takes place suggests a thermal gradient of about 1°C/mm around the periphery of the gut. The data emphasize the influence of blood flow on the temperature distributions obtained with water-bath heating, and illustrate the influence of biological factors on temperatures reached in heating by means of a water bath.

MEASUREMENT OF THE ELECTRICAL PROPERTIES OF MATERIALS OF BIOLOGICAL INTEREST

By R. J. Sheppard

Department of Physics,
Queen Elizabeth College, London

Complex permittivity and conductivity was briefly defined and explained with particular reference to biological materials. The reasons why such parameters and in particular their variation with frequency need to be known, were discussed. Apparatus required for such measurements was described.

The paper was then divided into two sections. The first described frequency domain techniques and covered a.c. bridges (10 kHz–100 MHz), coaxial lines (50 MHz–12 GHz) and finally waveguides which can operate over narrow frequency bands up to about 100 GHz. The above represents the latest stage in the development of traditional techniques. The second part of the paper described the new method of time domain spectroscopy (TDS), which enables data to be taken in the time domain. These data are then Fourier transformed to give permittivity as a function of frequency. The advantages of TDS are that it has a wide frequency response and can measure small (less than 1 ml) conductive samples. The technique is also ideally suited to measure tissue, as well as solutions. Finally some recent data on the lens of rabbit's eyes were presented.

RECENT DEVELOPMENTS IN MICROWAVE HEATING

By J. W. Hand

MRC Cyclotron Unit,
Hammersmith Hospital,
Du Cane Road, London W12 0HS

A short review was given of some microwave applicators which are likely to be useful for application of hyperthermia. In particular a waveguide applicator partially loaded with dielectric slabs in order to produce a uniform microwave field across part of the aperture was described. Heating patterns produced by such an applicator are of greater uniformity than those produced by direct contact microwave applicators operated in the TE_{10} mode. This new type of applicator could be of use in treating patients with superficial lesions. Also microwave applicators made from micro-miniature coaxial waveguide are reviewed. These applicators may be inserted into tissue via a catheter or as interstitial implants and are capable of producing localized hyperthermia deep in tissue. Small applicators of coaxial geometry could prove useful in the treatment of areas such as bladder, rectum, oesophagus and cervix.

The second part of this talk described an experimental technique for inducing hyperthermia in a loop of exteriorized mouse intestine. The organ is immersed in a liquid which is both biologically compatible with and dielectrically similar to this tissue. This technique improves the efficiency of coupling the microwaves into the tissue and avoids the effects of shape and size on the absorption characteristics of the irregularly shaped mouse jejunum.

Finally, a brief report was given on the development of a multi-sensor thermistor probe produced by thick film technology, designed and built in collaboration with the Department of Electronic and Electrical Engineering, University of Loughborough, for temperature measurements in the presence of electromagnetic fields.

A TECHNIQUE FOR PRODUCING LOCALIZED MEASURABLE HYPERTHERMIA IN SUPERFICIAL RAT TUMOURS USING RADIO-FREQUENCY CURRENTS

By P. B. Dunscombe and B. M. Backhouse

Departments of Medical Physics and Radiotherapy,
Charing Cross Hospital, London W6 8RF

By means of a waveguide and aerial system, currents at 433 MHz have been passed through superficial tumours of rats to produce localized hyperthermia. It is to be expected that such a technique will result in higher rates of heat production in fat and in the regions near the electrodes. The latter effect has been demonstrated experimentally. Both the tumour and the rectal temperatures have been monitored during heating using thermocouple probes. The tumour probe was housed in a 26G steel needle to facilitate insertion into the tissue. By maintaining the metallic components of the probes normal to the electric vector of the field it was possible to reduce pick up of the electro-magnetic field to an acceptably low level. Thermographic studies performed on tissue-equivalent gels indicated a high degree of localization of heat production (full width at half maximum height of the temperature distribution was 1.5 cm) and also the surface heating effect already mentioned. Similar studies failed to show any perturbation of the temperature distribution due to the presence of a thermocouple probe. A series of anaesthetized rats carrying tumours on the flank was subjected to the heating system. The mean rate of rise of temperature in the tumours was $3.3 \pm 2.2^{\circ}\mathrm{C\ min}^{-1}$ at 37°C corresponding to a power absorption of $270 \pm 190\mathrm{W\ kg}^{-1}$.

HEAT TRANSFER AND CONDUCTION IN RADIO-FREQUENCY HEATING

By R. Strang and J. Patterson

West of Scotland Health Boards,
Department of Clinical Physics and Bioengineering,
11 West Graham Street, Glasgow G4 9LF

Radio-frequency capacitive heating has been used for several decades in physiotherapy and has recently become of interest in clinical and experimental investigations into the use of hyperthermia as a means of cancer therapy. In this heating modality the tissue to be heated is placed between two electrodes and a high-frequency alternating current is passed between them. The main advantage of this type of heating over other techniques is that it is possible to achieve heating at depth.

Several factors affect the distribution of temperature produced by this technique, including differences in electrical impedance and specific heat, conduction of heat out of the heated volume and the transfer of heat by blood flow. The effect of each of these has been studied.

Differences in electrical impedance and specific heat give rise to preferential heating in some tissues. In particular, if the tissues are in series, the relative temperature rise in fat and bone is much greater than in muscle (18:1 fat, 27:1 bone).

After heat is deposited in a tissue there are processes which modify the resulting temperature distribution. One such process is the flow of blood through the tissue. Blood flow has two main effects: (a) for a given rate of production of heat in a tissue the temperature produced is limited to a certain value dependent on the blood flow; and (b) the temperature subsequently produced in normal tissues varies widely due to the large range of blood flows encountered.

Conduction of heat out of the heated volume is another modifying process. Using a simple diffusion model it was shown that the conduction of heat is large enough to reduce the temperature significantly within a few centimetres of the edge of a heated tissue although it is too small to eliminate temperature gradients completely even over a distance of 1 cm.

The advantages and disadvantages of radio-frequency heating were discussed and further study of some of the physical and physiological factors involved was emphasized.

ULTRASONIC HYPERTHERMIA: A FEASIBILITY STUDY

By G. R. ter Haar

Institute of Cancer Research,
Sutton, Surrey

Ultrasonic interaction with tissue can be divided broadly into two categories: thermal and non-thermal (mechanical) effects. The heating effect of ultrasound means that localized temperature rises over closely defined volumes may be achieved. The attenuation coefficients of fat, muscle and bone are 0.6, 1–4, and about 20 dB cm^{-1} MHz^{-2} respectively. Thus, in soft tissue, heating is greatest in muscle. Using focussed ultrasonic beams, small (less than 1 mm diameter) focal regions may be heated.

Temperature distributions arising from a plane ultrasonic wave incident on a plane-faced tissue slab of fat/muscle/bone have been calculated. The distributions demonstrate the necessity for accurate knowledge of acoustic attenuation coefficients and of the reflection occurring at tissue interfaces. Using therapeutic levels of ultrasound (less than 3 W cm^{-2}, 1 MHz) temperature rises of up to 12°C are predicted in muscle.

ATHERMAL EFFECTS OF MICROWAVES AT THE CELLULAR LEVEL

By N. W. Ramsey

Medical Physics Department,
Charing Cross Hospital, London W6 8RF

Many investigations of the biological effects resulting from the absorption of UHF radiation, in the absence of a temperature rise, have been made. Few authors have related observations to the amount of energy absorbed, the incident power usually being given in mW/cm^2. This situation reflects the difficulty of quantifying the absorption of UHF radiation in tissues, particularly in the whole animal. The following observations relate to experiments in which it was claimed that thermal effects were excluded.

Cataract formation was induced in the lens of rabbit eyes (Carpenter *et al.*, 1960) by exposure to 12.2 cm wavelength radiation. A roughly reciprocal relationship was found between incident power and exposure time required, but at less than 40 mW/cm^2 incident power, virtually unlimited exposure could be tolerated. Using 1.25 cm wavelength (Gunn *et al.*, 1960) it was found that an exposure of five minutes duration was sufficient to impair production of testosterone in the rat testes even though histological examination revealed no obvious damage. This treatment produced a slight temperature rise but a comparable temperature rise induced by exposure to infrared radiation did not impair testosterone production. The absorbed power in these experiments was less than 250 mW/cm^2. Embryonic chick hearts (Paff *et al.*, 1963) exposed to 1.25 cm wavelength radiation at an incident power of 74 mW/cm^2 and for durations up to three minutes showed gross changes in the ECG pattern. Evoked potentials were recorded from an electrode in the brain stem of a cat (Frey, 1967) exposed to pulsed radiation at 20 cm to 25 cm wavelength, and peak power level of 60 mW/cm^2. The effect of 12.2 cm radiation on the intercellular reaction between mouse macrophages and a suspension of human erythrocytes was to depress phagocytosis. The effect was found to be transient, recovery taking place when the irradiation ceased. The incident power level was 50 mW/cm^2 with exposures lasting up to 30 minutes.

Erythrocytes from rabbit venous blood and granulocytes isolated from the peritoneal cavity of the rabbit, following exposure to 10 cm wavelength radiation *in vitro* (Baranski *et al.*, 1973) showed evidence of damage. An incident power of less than 10 mW/cm^2 for a period of one hour was sufficient to produce a loss of potassium from erythrocytes, the authors interpreting this as indicating interference with the sodium-potassium pump. Haemoglobin loss from the erythrocytes occurred at an incident power of less than 10 mW/cm^2, and the osmotic resistance of the lymphocytes indicated some degree of cell damage for a similar exposure. Incident powers as low as 5 mW/cm^2 for periods of less than one hour were sufficient to kill a proportion of granulocytes, as demonstrated by staining with nigrosin.

If cells in the blood are readily damaged by such low power levels, the implications could be far reaching because of the fact that however radiation may be applied to the body, some fraction of the blood will always be irradiated. Carefully quantitated data on the athermal effects of UHF on intact animals is an essential prerequisite to the use of UHF heating for the production of hyperthermia in humans.

REFERENCES

Baranski, S., Szmigielski, S., and Moneta, J., 1973. Effects of microwave irradiation in vitro on cell membrane permeability. Biologic Effects and Health Hazards of Microwave Radiation. Proceedings of an International Symposium, Warsaw, 173.

Carpenter, R. L., Biddle, D. K., and Van Ummersen C. A. 1960. Opacities in the lens of the eye experimentally induced by exposure to microwave radiation. *IRE Transactions on Medical Electronics ME–7*, 152–157.

Frey, A. H., 1967. Brain stem evoked responses associated with low intensity pulsed UHF energy. *Journal of Applied Physiology*, *23*, 984–988.

Gunn, S. A., Gould, T. C., and Andersen, W. A. D., 1960. The effect of microwave radiation on the male endocrine system of the rat. *Proceedings of the 4th Annual Tri-Service Conference on the Biological Effects of Microwave Radiation*, *1*, 99–115.

Paff, G. H., Boucek, R. J., Nieman, R. E., and Deichfamm, W. B., 1963. The embryonic heart subjected to radar. *Anatomical Record*, *147*, 379–385.

THE RESPONSE TO COMBINED HYPERTHERMIA AND RADIATION OF AN EXPERIMENTAL MAMMARY CARCINOMA AND ITS SURROUNDING NORMAL TISSUE

By J. Overgaard

The Institute of Cancer Research,
Radiumstationen, DK–8000 Aarhus C, Denmark

The effect of combined hyperthermia and radiation on solid tumours is produced by two different mechanisms. One is a hyperthermic radiosensitization and the other is a direct cytotoxic effect of heat, which may preferentially destroy cells situated in the tumour core where a different environment exists (low pH, hypoxia and malnutrition).

In order to optimize the therapeutic effect of the combined hyperthermia–radiation treatment of solid tumours, the influence on local tumour control and on normal tissue damage was studied during variations of heating time, temperature and the sequence and interval between the two modalities.

As a model a mouse mammary carcinoma transplanted into the feet of C3D2F1 mice was used. Hyperthermia was produced by placing unanaesthesized mice in a special jig which allowed immersion of the tumour-bearing foot into a temperature-controlled water bath. Radiation was given either before, during or after heating. The results of the different regimens were evaluated as the radiation dose required for 50% tumour control at 120 days (TCD50) or the radiation dose required to achieve moist desquamation in 50% of the treated feet (DD50).

An increasing thermal enhancement ratio (TER) was observed with increasing temperatures between 41.5°C and 44.0°C. This was true for both tumour and normal tissue response and no improvement in therapeutic gain could be found by varying the temperature if radiation and heat treatment was given simultaneously.

Initially, all heat treatment was given for one hour. However, variation in heating time at different temperature levels did not alter the therapeutic ratio if radiation and heat treatment was simultaneous.

Different results were obtained by using an interval between the two modalities. Hyperthermic treatment given with intervals up to 24 hours before radiation showed (except for the 24-hour interval) no improvement in the therapeutic ratio as the enhancement of normal tissue damage was similar to the increased tumour response. However, if radiation was given before the heat, the normal tissue showed rapid recovery, and after four hours the normal tissue damage did not exceed that observed after radiation alone. In contrast, the tumour effect was still enhanced by a factor of about 1.5. This enhancement was lower than that seen after simultaneous treatment (about 1.8–2.0). This difference in tumour and normal tissue response persisted with intervals of up to 24 hours between the treatment modalities. Based on these studies the optimal therapeutic ratio seemed to require a regimen in which radiation was given several hours before hyperthermia. The data indicate that the important tumour effect was hyperthermic cytotoxicity rather than hyperthermic radio-sensitization as this seems to occur to the same degree in the normal and malignant tissue.

THERMAL ENHANCEMENT RATIO AND THERAPEUTIC GAIN IN SEVEN EXPERIMENTAL MOUSE TUMOURS

By Sally A. Hill, Fiona A. Stewart and Juliana Denekamp

Gray Laboratory, Mount Vernon Hospital,
Northwood, Middlesex HA6 2RN

The combined effects of hyperthermia and irradiation have been tested in seven different types of transplantable mouse tumour, using delay in tumour regrowth as the measure of response. When the heat dose (42.5°C for one hour) was applied immediately before or after irradiation, the thermal enhancement ratio varied between 1.0 and 1.7 for the range of tumours tested. These values were compared with the range of normal tissue data from the literature and in all cases a therapeutic loss was indicated, the sensitization in the normal tissues being equal to or greater than that in the tumours.

As the time interval between the two treatments was increased there was some loss of thermal sensitization in the tumours, with the response being somewhat more variable when heat preceded the X rays. This loss of effect occurred more slowly in the tumours than in similarly treated mouse skin, so that a therapeutic advantage was seen when the two treatments were separated by a few hours.

COMBINED X RAYS AND HYPERTHERMIA: LOSS OF THERAPEUTIC ADVANTAGE WITH FRACTIONATION

By Fiona A. Stewart and Juliana Denekamp

Mount Vernon Hospital,
Northwood, Middlesex HA6 2RN

A mouse fibrosarcoma and the skin of the mouse foot were used as models to measure thermal sensitization to X-irradiation.

For single doses, when heat (42.5°C/1 h) was applied immediately after X rays the thermal enhancement ratios (TERs) of skin and tumour were similar, indicating no therapeutic advantage. However, if heat was applied two to six hours after X rays the TER was much greater for tumour than for skin, giving a therapeutic gain.

A series of fractionated experiments was therefore designed using the tumour and skin models, to measure TER when heat (42.5°C/1 h) was applied immediately or at three hours after each X-ray fraction.

For the *skin* there was a large TER of 1.6 to 1.7 when heat was applied immediately after X rays in both two and five fractions treatment. The TER was reduced (1.0 to 1.1) if heat was not applied until three hours after X rays.

For the *tumour* there was no TER for two fractions either with heat immediately or at three hours after X rays. For the five fraction schedule a small TER of 1.1 to 1.3 was measured with heat immediately after irradiation.

None of the fractionated schedules tested gave a larger thermal enhancement for tumour than for skin; there was therefore no therapeutic advantage with the fractionated treatments tested for this tumour.

Results obtained from the hyperthermia studies were compared with single-dose, two and five fraction studies using neutrons, or X rays plus misonidazole. The most effective treatments were those involving misonidazole. Neutrons or X rays combined with hyperthermia gave no therapeutic advantage.

INCREASE IN DIFFERENTIAL RADIOSENSITIVITY BETWEEN TWO CHINESE HAMSTER CELL LINES AFTER HYPERTHERMIC PRETREATMENT

By H. Schlag and Christine Lucke-Hühle

Kernforschungszentrum Karlsruhe,
Institut für Genetik und für Toxikologie von Spaltstoffen,
Germany

Hyperthermia in combination with ^{60}Co γ therapy not only increases the radiosensitivity of mammalian cells, but can also create a greater selectivity between individual cell populations.

Survival and cell cycle alterations in two established Chinese hamster cell lines (V79 and B14F28) were examined after exposure to ^{60}Co γ radiation, hyperthermia at 42°C and after the combination of both treatments.

V79 and B14F28 cells showed a similar radiosensitivity at 37°C. They exhibited, however, a marked difference in their response to ^{60}Co γ rays if they were pretreated with mild hyperthermia (one hour at 42°C): A dose of 400 rad of ^{60}Co γ rays alone killed about 50% of each cell type, while the same dose delivered in combination with hyperthermia killed 60% of the B14F28 cells and about 98% of the V79 cells.

Heat alone also caused cell death and cell cycle changes to a different extent: exponentially growing V79 cells were much more thermosensitive: four hours at 42°C decreased survival to 1.3% whereas 70% of the B14F28 survived this treatment. Cell cycle analysis by flow-microfluorometry demonstrated a block in G_2+M for both cell types. However, while B14F28 cells traversed S-phase without any obvious prolongation, V79 cells accumulated in S-phase during heat treatment, an effect which seems to be related to cell death.

The differential response of the two Chinese hamster cell lines to hyperthermic killing and thermal radiosensitization is comparable to the different RBE values obtained for both cell lines after high-LET irradiation (π-mesons).

METASTASES AND IMMUNOLOGICAL STUDIES IN C_3H MICE AFTER HYPERTHERMIA

By A. S. Abdelaal, Susan M. Chamberlain, A. H. W. Nias and Agnes Walker

Glasgow Institute of Radiotherapeutics and Oncology,
Belvidere Hospital, Glasgow G31

We have examined the response to hyperthermia of a carcinoma in C_3H mice and report a dramatic promotion of metastasis by local heating administered in time-temperature combinations sufficient to eradicate the primary tumour (*e.g.* one hour at 43.5°C).

The carcinoma originated as a spontaneous mammary tumour in 1974 and has been serially transplanted ever since. The volume doubling time is about one day at the size of 6 mm diameter when treatments are given. The tumour is poorly differentiated and contains many foci of necrosis. The very high radiation TCD_{50} value of 67.5 Gy is compatible with this evidence of extensive hypoxia.

The cell-mediated immunological response of the mice has been assessed using the PHA response of splenic lymphocytes. The PHA index was significantly reduced in tumour-bearing mice but returned towards a normal value after successful treatment of the primary tumour by either surgical excision, radiotherapy or hyperthermia. The PHA index remained low, however, in a number of the mice which had to be sacrificed earlier than 100 days after hyperthermia with the tumour locally controlled. Histological examination revealed pulmonary and other blood borne metastases in these mice.

The incidence of metastasis was 25% after local hyperthermia, significantly higher than the 10% rate after local radiotherapy ($P = <0.04$).

SOME EFFECTS OF HEAT ON RED BLOOD-CELL MORPHOLOGY

By W. T. Coakley, L. A. Crum, J. O. T. Deeley, and A. J. Bater

Department of Microbiology, University College,
Cardiff

Studies of the effect of elevated temperatures on the response of human erythrocytes to flow stress will be reviewed. We describe a system for the controlled heating of erythrocytes on a microscope stage. The influence of heating rate, proximity of boundaries, local liquid flow and mechanical shock on the type of morphological change observed at 48°C (near the transition temperature of spectrin) was examined. ATP pool size did not fall during heating. The diacyglycerol content of the membrane increased. The patterns of fragmentation of the erythrocytes have features which suggest the expression of liquid-like properties of the cell and its membrane when the form-maintaining structures such as spectrin are weakened.

THE INFLUENCE OF COMBINED HYPERTHERMIA AND GAMMA IRRADIATION ON DIFFERENT *in vivo* CELL POPULATIONS

By H-J. Weber, W. Porschen, and L. E. Feinendegen

Nuclear Research Center Jülich GmbH, P.O. Box 1913
5170 Jülich, Germany

By F. Dietzel

Justus-Liebig-Universität, Center for radiology,
63 Lahn-Gießen, Germany

The effect of gamma irradiation, hyperthermia and combined treatments on euoxic and average tumour cells (sarcoma 180) was studied by sequentially labelling the tumour-bearing NMRI mice with 5-iodo-2′-deoxyuridine, a thymidine analogue carrying either ^{125}I or ^{131}I. First $^{125}IUdR$ was injected intravenously followed 50–70 hours later and prior to treatment by $^{131}IUdR$. Thus at the time of treatment the average tumour cell population was already labelled by $^{125}IUdR$, whereas $^{131}IUdR$ nearly exclusively tagged the perivascular euoxic tumour cells. A large proportion of average tumour cells is considered to be hypoxic. IUdR is stably bound to DNA, reutilization is minimal and so the measured loss of activity from the tumour more than 80 hours after labelling indicates cell loss or cell lysis.

The radiation-induced loss of activity from the two labelled tumour-cell populations indicate that ^{60}Co γ rays mainly affected euoxic cells. The enhancement ratio, probably the oxygen enhancement ratio, is about 2.0.

Hyperthermia (42°C) almost exclusively affects the average cells. When 10 Gy γ rays and hyperthermia were combined the enhancement ratio was larger if hyperthermia was given after irradiation.

At dose levels from 5–20 Gy the dose modifying factors (DMF) for 60 min hyperthermia (42°C), evaluated from cell loss rates, were in the range from 2.9 at 5 Gy to 2.1 at 20 Gy. Based on tumour regression 100 days after treatment, DMFs of 1.2 at 15 min hyperthermia up to 3.0 at 120 min hyperthermia after 10 Gy γ rays were observed.

When evaluated from cell loss rate, tumour regression, tumour growth delay and TCD 50/100, misonidazole (500 mg/kg body weight), applied 15 min before gamma irradiation, gave a DMF of 1.47, hyperthermia (42°C, 60 min) immediately after 10 Gy gamma irradiation gave a DMF of 2.75 and the triple scheme Misonidazole plus 10 Gy gamma irradiation plus hyperthermia increased the DMF to 3.1.

IN VIVO ASSAY OF THE RADIATION SENSITIVITY OF EUOXIC AND HYPOXIC TUMOUR CELLS; INFLUENCE OF γ RAYS, CYCLOTRON NEUTRONS, HYPERTHERMIA AND MIXED MODALITIES

By W. Porschen, H-J. Weber, H. Muhlensiepen and L. E. Feinendegen

Institut fur Medizin,
Kernforschungsanlage Jülich GmbH.,
D-517 Jülich, Postfach 1913, Germany

It is the objective of this *in-vivo* study to measure quantitatively, by external means, the effect of experimental tumour therapy on tumour cell lysis in living mice. Iododeoxyuridine (IUdR) is used as specific DNA-precursor. By sequentially labelling the tumour-bearing animals with $^{125}IUdR$ and $^{131}IUdR$ 50 hours apart, the average tumour cells at the time of the second injection are labelled by

^{125}IUdR and the euoxic tumour cells are specifically labelled with ^{131}IUdR. Tumour treatment at this stage of labelling permits the observation of the reaction of euoxic cells and average tumour cells and finally yields data on hypoxic cells and thus on the oxygen enhancement ratio. This information adds to results from tumour control and growth delay.

With this technique, effects were analysed of ^{60}Co γ rays, cyclotron neutrons ($\bar{E}$ 6 MeV), hyperthermia (42°C water bath), Misonidazole (500 mg per kg body weight), or combinations of these. Misonidazole (15 min before irradiation) gave a dose modifying factor (DMF) of 1.5 for γ rays and of 1.1 for neutrons.

When evaluated from tumour growth delay and TCD–50/100, misonidazole gave a DMF of 1.47 for γ rays and of 1.27 for neutrons.

Based on percent tumour regression 100 days after treatment, the DMF from hyperthermia (after irradiation) was 2.75 for γ rays (at 10 Gy) and 2.2 for neutrons (at 3.2 Gy). For γ rays or neutrons the DMF with misonidazole and hyperthermia was about 3.1 or 2.4 respectively.

These findings demonstrate that local irradiation effects on tumours from cyclotron neutrons may be modified by local hyperthermia and/or hypoxic sensitizers.

SINGLE OR FRACTIONATED HYPERTHERMIC TREATMENT OF MALIGNANT AND NORMAL TISSUE

By J. Overgaard and H. D. Suit

The Institute of Cancer Research, Radiumstationen,
DK–8000 Aarhus C. Denmark, and
Massachusetts General Hospital and Harvard Medical School,
Boston, Ma. 02114, U.S.A.

The effect of single and fractionated hyperthermia after water-bath heating was studied in a methylcolanthrene-induced fibrosarcoma (FSa) isotransplanted into the feet of C_3H mice.

The time-temperature relation for TCD50 (50% tumour control dose) after a single treatment in the temperature range 41.5–45.5°C was found to show a log-linear relationship which tended to approach a modified Arrhenius plot. At temperatures above 43°C the heating time to obtain TCD50 was reduced by half for each 1°C increase in temperature. At temperatures below 42.5°C the curve was steeper with a tendency to double the treatment time for each half degree reduction in temperature.

The damage to normal tissue in the tumour-bearing foot was estimated at two levels with a DD50 assay (50% damage dose). Severe normal tissue damage was obtained at higher heat doses than was necessary for tumour control but showed a time–temperature relationship similar to the tumour response, thus indicating no variation in therapeutic ratio at different temperatures.

This time–temperature relation is similar to other observations in tumour and normal cells heated *in vivo* and *in vitro* and points to a general time–temperature relationship for hyperthermic damage.

The recovery from thermal damage was also studied. Tumours were treated in a water bath with two equally large fractions of heat given with intervals at 0, 2, 6, or 24 hours. Temperatures of 42.5°, 43.5° and 44.5°C were investigated.

The results showed a slow and parallel recovery in both tumour and normal tissue. After two or six hours interval the overall treatment time was not longer than for a single heat exposure. After 24 hours interval a moderate repair was noticed, but more than 50% of the heat damage was still present in both tumour and normal tissue. Interestingly the two-hour interval was associated with an overall treatment time which was shorter than that seen after a single treatment. It seems likely that this is due to changes induced by the first fraction in the tumour and in the surrounding tissue which may increase the sensitivity of the tissue to a subsequent heat treatment. Owing to the parallel recovery found in tumour and normal tissue no variations in therapeutic ratio could be obtained by using a fractionated heat treatment.

Modified Arrhenius plots of the time–temperature relation for thermal tumour damage showed no difference with the fractionated schedules from that seen after a single treatment.

The dose response curves tend to become less steep with increasing time interval which may reflect the presence of a slight thermal tolerance.

THE ROLE OF GLUCOSE INFUSION IN HYPERTHERMIA

By M. von Ardenne

Forschunginstitut Manfred von Ardenne,
Dresden, East Germany

In this report concerning the present state of multiple-step therapy of cancer we focus our attention on the shift of tissue pH towards the acid region following a prolonged infusion of glucose. The aim is to optimize the effect of selective hyperthermia in cancerous tissues induced by the application of homogeneous energy inputs to body regions according to the two-step CMT-Selectotherm procedure. Some 150 minutes after these procedures are applied, there is a selective change in the blood microcirculation in cancerous relative to normal tissues. The multiple consequences of this effect are discussed. A stoppage of the circulation can be achieved by short duration application of local hyperthermia at 42.5°C. The changes which should be made to the concept of the multi-step therapy of cancer apply only to the timing. It will be emphasized that the findings create a new situation in the multiple-step therapy of cancer which is challenging and requires investment of considerable effort into both animal experiments and clinical studies.

A STUDY OF THERMAL DAMAGE BY TIME LAPSE CINEMICROGRAPHY

By Helen Bass and J. L. Moore

Tenovus Laboratories, Velindre Hospital,
Whitchurch, Cardiff

W. T. Coakley and L. A. Crum

Department of Microbiology, University College,
Cardiff

In previous studies of Chinese hamster ovary cells (CHO–K1) exposed to lethal thermal stress at 43°C, scanning electron micrographs have revealed a number of morphological changes. Following heating for three hours the cells become rounded, and their surfaces undulate showing many blebs and ruffles and there is a decrease in the number of microvilli (Bass *et al.*, 1978).

In the present paper, we describe a time-lapse cinemicrography study of the development of the ultrastructural changes. The cells were heated to 57°C to accelerate the rate of those changes observed at 43°C. Initially, the cytoplasm is drawn towards the centre of the cell and becomes more granular in appearance. There is partial separation of the granular cytoplasm from the plasma membrane. After a time blebs filled with a homogeneous fluid develop on the cell surface. Occasionally there is some Brownian motion inside the bleb but it appears that the microfilament network of the cells remains sufficiently intact to prevent many organelles from entering the blebs. Blebs often detach from the cells. Some adjacent surface-bound blebs fuse.

REFERENCE

BASS H., MOORE, J. L., and COAKLEY, W. T., 1978. Lethality in mammalian cells due to hyperthermia under oxic and hypoxic conditions. *International Journal of Radiation Biology*, *33*, 57–67.

THE INTERACTION OF RADIATION AND HYPERTHERMIA IN AN EUKARYOTIC MICROBIAL MODEL SYSTEM

By J. Kiefer

Strahlenzentrum der Justus-Leibig-Universität Giessen,
Leihgesterner Weg 217, D-6300 Giessen, Germany

The interaction of treatment with elevated temperatures (37–50°C) and X irradiation was studied in diploid yeast. If heat preceded X-ray exposure there was a significant sensitization but no change in the oxygen enhancement ratio (OER). When heat was given after X rays, however, a reduction of the OER occurred from its normal value of 2 to about 1.4. Further studies revealed that heat affects mainly those processes which are responsible for the recovery from potentially lethal damage. Biochemical experiments suggest that protein biosynthesis is extremely sensitive to heat and that this pathway may play a significant role in the reported effects.

THE INFLUENCE OF pH ON THE ENHANCEMENT OF RADIATION DAMAGE BY HYPERTHERMIA

By J. Lunec and R. Parker

MRC Cyclotron Unit, Hammersmith Hospital,
Du Cane Road, London, W12 0HS

HeLa-S3 cells were treated in suspension with combinations of heat at 44°C and irradiation with 7 MeV electrons, both in medium of pH 7.4 and pH 6.7. Irradiation followed heat treatment with a time lag of less than five minutes. The medium was buffered with 0.02M HEPES and the pH was adjusted to the desired level by adding Na0H. Cell survival after treatment was assessed by colony forming ability.

When the temperature of the cells was maintained at 44°C for ten minutes no cell killing was observed with the heat treatment alone, either at pH 6.7 or pH 7.4. A heat dose of 44°C for ten minutes was found to enhance the cell killing produced by subsequent doses of radiation, and the degree of enhancement was found to be the same at pH 6.7 as at pH 7.4.

A heat dose of 44°C for 30 minutes killed approximately 60% of the cells at pH 7.4 and 90% of the cells at pH 6.7. When the heated samples were subsequently exposed to radiation the number of cells surviving the combined treatment fell exponentially with increasing dose of radiation with no shoulder on the radiation survival curve either at pH 7.4 or pH 6.7. After being heated the cells surviving at pH 6.7 were more sensitive to subsequent irradiation than cells surviving at pH 7.4. The difference in radiosensitivity may be due to the induction of different degrees of synchrony by the heat treatment at these two values of pH.

THE RESPONSE OF CANCER CELLS TO HYPERTHERMIA AT LOW pH

By J. A. Dickson

Cancer Research Unit,
Department of Clinical Biochemistry,
Royal Victoria Infirmary, Newcastle upon Tyne

Von Ardenne has postulated that hyperglycaemia of 400 mg% in a tumour-bearing host leads to a selective increase of glycolysis in the tumour, with a resultant rise in the concentration of tumour lactic acid and decrease in intracellular pH (pH_i). Labilization of the lysosomal membrane ensues and activation of the released lysosomal enzymes leads to destruction of the cancer cells. The lysosomal damage is potentiated by hyperthermia. Optimal conditions for this chain-reaction are a pH_i in the region of 6.4 plus heating at 40° for 200–300 min. Overgaard has postulated that the same destructive chain-reaction may be initiated by a "relative" increase in glycolysis resulting from inhibition of respiration in heated cancer cells.

Intracellular pH of tumour cells was measured from partitioning across the cell membrane of the weak organic acid 5,5-dimethyl-2, 4-oxazolidinedione (DMO). *In vitro*, glycolysis of a rat breast cancer line was decreased at a measured pH_i of 6.4, and this pH did not potentiate the destructive effects of 42°C on the cells, measured by their ability to replicate.

In the Yoshida sarcoma in the rat, a mean blood glucose of 400 mg% led to a fall in tumour pH, measured by microcapillary electrode, from 7.19 to 6.6, but pH_i remained at 7.21. The fall in extracellular pH was accompanied by an increased lactic acid concentration in the tumour, possibly due to impaired clearance into the circulation. Curative hyperthermia (42°C for one hour) or four hour hyperglycaemia plus heat did not alter pHi and tumour regression time was not affected by the combined treatment. Hyperglycaemia led to a decrease in tumour glycolysis.

The data do not support the chain-reaction hypothesis centering on decreased pH_i; the reported sensitivity of heated cancer cells to decreased external pH *in vitro* may involve damage to the cell membrane or other components, and may not require a decrease in pH_i as the major event.

THE EFFECTS OF HYPERTHERMIA ON LYSOSOMAL ENZYME ACTIVITY IN SOLID TUMOURS AND IN CULTURED CELLS

By G. M. Barratt, M. Keech and E. D. Wills

Department of Biochemistry and Chemistry,
The Medical College of St. Bartholomew's Hospital,
Charterhouse Square, London EC1M 6BQ

Lysosomes contain many hydrolytic enzymes capable of digesting virtually every cellular component and their leakage into the cytoplasm of cells could cause extensive cellular damage. We have studied the activity of typical lysosomal enzymes after treatment of cells by hyperthermia in an attempt to evaluate the role of lysosomal enzymes in tumour regression using transplanted C_3H mouse mammary tumours and HeLa cells. Quantitative histochemical methods have been employed.

The activity of acid phosphatase, used as a marker lysosomal enzyme for HeLa cells, increased when the cells were subjected to short incubation periods (30–90 min) at temperatures between 41° and 45°. Decrease of pH increased the effects of elevated temperatures. Lysosomal acid phosphatase activity and β-glucuronidase activity were also studied in transplanted mouse mammary tumours subjected to temperatures of 41.5°–43.5°C for one hour *in vivo*. Increased lysosomal enzyme activity was observed immediately after hyperthermic treatment, but 24 hours after treatment the enzyme activity returned to normal control values.

Irradiation also causes activation of lysosomal enzymes of HeLa cells and mammary tumour but, unlike hyperthermic treatment, effects are not observed until several hours after irradiation; it may therefore be concluded that hyperthermia and irradiation cause lysosomal enzyme activation by two entirely different mechanisms.

THERMAL TOLERANCE *IN VIVO*

By Marilyn P. Law

MRC Cyclotron Unit, Hammersmith Hospital,
Du Cane Road, London W12 0HS

The response of tissues to hyperthermia, applied alone or combined with X rays, is reduced if treatment is fractionated. This effect could be related to thermal tolerance induced by the first heat treatments.

The mouse ear was used to investigate the effect of a priming heat treatment on subsequent hyperthermia alone or combined with X rays. Heating was by immersion in hot water.

Priming heat treatments of 2–40 min at 43.5°C induced transient resistance to a second heat treatment at 43.5°C (thermal tolerance). At maximum tolerance, observed one day after a 20 min priming treatment, the heating time to cause necrosis in 50% of the ears heated had to be increased from the single treatment of 50 min to 120 min, an increase by a factor of 2.4. Shorter priming treatments induced less thermal tolerance.

A priming heat treatment of 40 min at 43.5°C reduced the skin response to combined heat and X rays given 2–4 days later. Thermal enhancement ratios for heat treatments of 30 min at 42.5°C or 43.5°C given immediately before X rays decreased from 1.6 or 2.9 without priming treatment to 1.4 or 2.3 with priming treatment. The changes in TER were equivalent to changing the temperature by 0.5°C or the heating time by a factor of 1.7. This effect is less than the induced thermal tolerance to heat alone.

THERMAL TOLERANCE AND DRUG CYTOTOXICITY *IN VITRO*

By J. E. Morgan, D. J. Honess and N. M. Bleehen

Department of Clinical Oncology and Radiotherapeutics,
Addenbrookes Hospital, Cambridge CB2 2QQ

We have investigated thermal tolerance *in vitro* using EMT6 tumour cells treated either with hyperthermia alone or in combination with a cytotoxic agent.

Preheating cells at 40°C for several hours has been shown to result in protection from a subsequent one hour exposure at 43°C. Thermal tolerance appeared to reach a plateau level under these conditions after three hours preheating. A similar time course for the development of protection from subsequent heat treatment at 43°C was seen using preheat temperatures of 39°C and 41°C.

Preheating for three hours at 40°C has been found to effect the response of the cells to a subsequent one hour exposure to a cytotoxic agent at 43°C. Three drugs have been used: bleomycin, BCNU and adriamycin, all of which are potentiated in their cytotoxicity by hyperthermia. With both BLM and BCNU, preheating resulted in a greater increase in surviving fraction than expected, assuming the same level of heat protection as seen in the absence of drug, but with ADR the surviving fractions were reduced below the expected levels. For all three drugs, the differences between the observed and expected levels of survival for preheated cells were shown to be highly significant using an analysis of variance technique. It was, therefore, concluded that there was some form of interaction occurring between preheat protection and drug cytotoxicity.

Preheating for three hours at 40°C, which alone resulted in no significant cell killing, was found to have no apparent effect on the subsequent response of the cells at 37°C to a one hour exposure to any of the three drugs used.

TWO QUALITATIVELY DIFFERENT EFFECTS OF HYPERTHERMIA ON LYSOSOMAL ENZYME ACTIVITY IN MOUSE SPLEEN

By S. P. Hume, M. A. Rogers and S. B. Field

MRC Cyclotron Unit, Hammersmith Hospital,
Du Cane Road, London W12 0HS

A quantitative histochemical technique has been used to study the effects of hyperthermia on lysosomal acid phosphatase activity in normal tissue. Hyperthermia, induced by hot water immersion, causes a rapid lysosomal response in both spleen and kidney in the mouse and in tail cartilage in the baby rat. Only the splenic response has been studied in detail.

Two qualitatively different responses are observed, dependent on the severity of the treatment. We have related these two effects to two of the effects of heat on tissues, namely (1) the transient ability of heat to potentiate X-ray damage and (2) the irreversible cell-killing effect of severe hyperthermia. Heating to temperatures below 42.5°C causes a transient increase in acid phosphatase activity with no observable change in lysosomal membrane permeability. This variation in activity corresponds very well with the potential enhancement of radiation damage, both in temperature dependence and in the temporal relationship between heating and irradiation. The results suggest that hyperthermic treatments which cause no observable tissue damage may cause a transient effect at the subcellular level (reflected in lysosomal enzyme activation) which sensitizes the cells to radiation injury. Heating to temperatures above 42.5°C results in an immediate increase in lysosomal membrane permeability which may be related to direct cell killing by hyperthermia.

The phenomenon of induced thermal resistance was used as a test of the above hypothesis. A priming heat treatment has previously been shown markedly to affect the tissue necrosis response to subsequent severe hyperthermia, whilst having little effect on the ability of moderate hyperthermia to potentiate X-ray damage. Using a priming heat treatment of 41.8°C for 60 min, induced thermal resistance can be demonstrated for the lysosomal membrane effect. The degree of induced resistance observed is similar to that reported for the cell-killing effect and occurs over the same time course. The enzyme activation effect is unaltered by the priming heat treatment, as would be expected if enzyme activation is related to the X-ray potentiating effect of hyperthermia.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (*i.e.* April 20, for June edition).
Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiobiology Meetings

The following meetings are scheduled at the Institute: "The combination of radiotherapy and chemotherapy", December 2, 1978. "Radiation chemists talk to biologists", January 19, 1979.

Titles and preferably brief abstracts of papers proffered for the January meeting should reach Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, by December 14, 1978.

Further information can be obtained from the General Secretary, British Institute of Radiology (01–935 6237).

CT and Ultrasonic Scanning in Radiotherapy Treatment Planning

A joint meeting of The British Institute of Radiology and the Hospital Physicists Association, will be held on Thursday, November 16, 1978 at the Royal Marsden Hospital, Sutton, Surrey.

Information and registration: HPA, 47 Belgrave Square, London SW1X 8QX.

NMG Imaging

An evening meeting organized jointly by The British Institute of Radiology, the Institute of Electrical Engineers and the Institute of Electronic and Radio Engineers, will be held on Thursday, November 16, 1978 at the Institute House, 32 Welbeck Street, London W1.

Information from the General Secretary, The British Institute of Radiology.

British Medical Ultrasound Society Annual Meeting and Exhibition

To be held November 27–28, 1978 at the Civic Centre, Newcastle upon Tyne.

Further details from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Problems of Benign and Malignant Bone Tumours

A joint evening meeting organized by the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, to be held on Friday, January 19, 1979, at the Royal Society of Medicine, London.

Speakers: Dr. Mary Catto, Dr. P. Jacobs, Mr. D. R. Sweetnam and Dr. G. E. Flatman.

Further information: contact the Royal Society of Medicine.

Radiation Biology for Part I F.R.C.R. (Radiotherapy and Oncology)

An intensive course in Radiation Biology will be held from January 22–26, 1979 inclusive. It is primarily intended for radiotherapists in training but it is also open to other students of radiation biology and experimental oncology. Lectures and demonstrations will be given by the staff of the Paterson Laboratories.

Details from: Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX.

Clinical Oncology Symposium on Thyroid Cancer

The Royal College of Radiologists will be holding a multi-disciplinary symposium on January 26–27, 1979. It will be held at 66 Portland Place, London W1N 4AD and is intended for senior registrars, consultants and research workers. Selected topics on the subject of thyroid cancer will be reviewed by authoritive speakers from the United Kingdom. The registration fee is £25.

Full details of the symposium can be obtained from the Meetings Secretary, Royal College of Radiologists, 28 Portland Place, London W1N 4DE.

New Radiopharmaceuticals Including ^{123}I

An all day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on Wednesday, February 14, 1979 at the Middlesex Hospital Medical School.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Imaging in Nuclear Medicine

An evening meeting to be held on Thursday, February 15, 1979 at The British Institute of Radiology, 32 Welbeck Street, London, W1, organized jointly by The British Institute of Radiology, the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology).

Further information contact the General Secretary, The British Institute of Radiology.

Workshop on the use of Computerized Tomographic Scanners in Radiotherapy

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proffered papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

1979 The British Institute of Radiology Annual Congress

The 37th British Institute of Radiology Annual Congress and Scientific Exhibition will be held at the Middlesex Hospital Medical School on April 26–27, 1979. Included in a programme of invited papers on diagnosis, therapy, radiological physics and nuclear medicine topics will be the

Presidential Address by Mr. W. M. Ross entitled *The Institute, yesterday and tomorrow*, and the Silvanus Thompson Memorial Lecture by Professor G. E. Adams on *Past, present and future of hypoxic cell sensitizers*.

Details and registration from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. G. B. Schofield, Medical Officer, British Nuclear Fuels Ltd., on *Biological control in a plutonium production facility* at The British Institute of Radiology, 32 Welbeck Street, London, W1 on Thursday, May 17, 1979.

INTERNATIONAL SYMPOSIUM ON INTERVENTIONAL RADIOLOGY

An E.A.R. Symposium, organized by the Portuguese Society of Radiology and Nuclear Medicine, will be held May 30–June 2, 1979 in the Algarve, Portugal.

Proposed sessions include vascular therapy; selective embolization and management; catheter implantation in chemotherapy and percutaneous treatments; ultrasonic guiding techniques and nuclear imaging as a guiding technique for biopsy and fluid aspiration.

For further information contact the Portuguese Society of Radiology and Nuclear Medicine, 123, 1.° Esq., Avenida Elias Garcia, Lisbon 1, Portugal.

INTERNATIONAL COURSE IN CHEST RADIOLOGY

International Course in Chest Radiology and other aspects of chest disease, Stockholm, Sweden, June 11–13, 1979.

Organized by the *Fleischner Society*, a non-profit organization in memory of Felix Fleischner, Harvard University, Boston.

Information and application forms from: Björn Nordenström, M.D., Professor of Radiology, c/o Reso Congress Service, S-105 24 Stockholm, Sweden.

NUCLEAR CARDIOLOGY

A workshop organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on June 20, 1979 at the Institute House.

Further information contact the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The L.H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Erratum

In the article "A comparative survey of multi-directional tomographic units by Dr. P. D. Phelps and Dr. A. J. Ashley, *British Journal of Radiology*, *51*, 438, it has been noted that in Table I the manufacturer of the Stratomatic should be C.G.R.

We apologize for this error.

The effect of misonidazole on lymphocytes.
M. G. Clare and C. A. Joslin
Care with radiosensitizers.
J. H. Hendry and M. L. Sutton
Design of tomographic equipment.
F. P. Greenwell
SI units.
G. E. Smythe
Maintenance of "Graf Pen".
R. J. Willetts
Medical iconography.
C. B. A. J. Puijlaert
The design of the detector and collimators of a hybrid scanner.
H. Propp
The design of the detector and collimators of a hybrid scanner.
E. Vauramo and A. Virjo
ICRP 1977 recommendations and handling of radionuclide generators.
A. Nagaratnam and A. R. Reddy
The discovery of X rays.
C. B. Smith
Obituary: F. R. Berridge. 932
Proceedings of the British Institute of Radiology. 933
Recent advances in hyperthermia research (May 11–12, 1978).
Forthcoming events and other notices. 941

Book reviews

Endometrial carcinoma and its treatment: the role of irradiation, extent of surgery and approach to chemotherapy 846
Grundlagen der medizinischen radiologie (The basis of medical radiology) 846
Ultrasound: its applications in medicine and biology 854
Gallium-67 imaging 854
Hip arthrography 857
Tomodensitométrie cranio-cérébrale (scanographie) 866
Xeroradiography in otorhinolaryngology 874
A practical approach to modern X-ray equipment 912

INSTITUTE OF UROLOGY
(University of London)
in association with the St. Peter's Hospitals

URO-RADIOLOGY WEEKEND

8th and 9th December 1978
To be held in the Lecture Theatre, Institute of Urology
172 Shaftesbury Avenue, London WC2H 8JE

Friday 8th December 1978 2.00–6.30 p.m. (including tea and sherry)

Topics to include:	Speakers:
Ureterocoeles	Mr. D. Innes Williams
Radiological and urological problems in paediatrics	Mr. P. G. Ransley Dr. A. R. Chrispin
Current views on urinary calculi	Dr. H. M. Saxton Dr. G. A. Rose
Uro-radiology quiz	

Saturday 9th December 1978 9.30 a.m.–4.00 p.m. (including coffee, lunch and tea)

C.T. in staging and management of bladder tumours	Dr. R. T. D. Oliver
Bladder deformity and displacement on the IVU	Professor T. Sherwood
Papillary necrosis	Dr. I. Kelsey Fry
The management of renal transplants and their complications	Mr. E. P. N. O'Donoghue Dr. F. D. Thompson Dr. M. J. Kellett
Uro-radiology practice – from London to the Provinces	Professor T. Sherwood

Fee: £20
Applications to the Secretary, Institute of Urology, 172 Shaftesbury Avenue London WC2H 8JE. Tel: 01–836 5361.

Application must be made in advance. Seating accommodation is limited and allocation of places will be in order of receipt of application.

VOL 51 NO 611 NOVEMBER 1978

The British Journal of Radiology

Contents

Page

Radiology now. The ten day rule—principles and practice. 843
J. H. E. Carmichael and C. K. Warrick

Radiologic manifestations of epidemic haemorrhagic fever with renal syndrome. 847
Yong Whee Bahk and Choon Yul Kim

Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage. 851
Z. F. Boulis, R. Dick and N. R. Barnes

Visualization of the cystic artery after injection of Pancreozymin. 855
Z. Chudáček

Hepatobiliary imaging: a comparison of ^{99}Tc^{m}-dihydrothioctic acid and ^{99}Tc^{m}-pyridoxylidene glutamate in the non-jaundiced patient. 858
R. E. Jenner, E. R. Howard, M. B. Clarke and J. J. Barrett

Hepatobiliary imaging: the use of ^{99}Tc^{m}-pyridoxylidene glutamate scanning in jaundiced adults and infants. 862
R. E. Jenner, E. R. Howard, M. B. Clarke and J. J. Barrett

Constancy of radiation output during diagnostic X-ray exposures. 867
G. M. Ardran, H. E. Crooks and R. Birch

Hyperbaric oxygen and radiotherapy. The Medical Research Council's Working Party. 875
Sir Brian Windeyer

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the bladder. 876
I. S. Cade, J. B. McEwen, S. Dische, M. I. Saunders, E. R. Watson, K. E. Halnan, G. Wiernik, D. J. D. Perrins and I. Sutherland

Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. 879
E. R. Watson, K. E. Halnan, S. Dische, M. I. Saunders, I. S. Cade, J. B. McEwen, G. Wiernik, D. J. D. Perrins and I. Sutherland

Hyperbaric oxygen: the Medical Research Council trials and their clinical significance. 888
S. Dische

Vascular permeability in the ears of rats after X-irradiation. 895
Marilyn P. Law and R. H. Thomlinson

The relationship between total dose, number of fractions and fraction size in the response of malignant melanoma in patients. 905
Shirley Hornsey

Technical note. 910
- Preparation of the colon prior to radiology—a comparison of the effectiveness of castor oil, Dulcodos and X-Prep liquid.
  A. Cargill and W. Hately

Case reports. 913
- Non-thrombotic occlusion of the cavernous carotid from subdural empyema.
  R. W. Katzberg and G. Griffiths
- Miliary pulmonary infiltrates and penicillamine.
  Jørgen Petersen and Inge Møller
- Bilateral pigmented villonodular synovitis of the hip.
  R. L. Eisenberg and M. W. Hedgcock
- Phaeochromocytoma diagnosed during barium meal.
  I. Beggs
- A giant retrofemoral Baker's cyst.
  K. O. A. Meurman, A. Luppi and M. J. Turunen

Short communications. 921
- Human whole body line-scan imaging by NMR.
  P. Mansfield, I. L. Pykett, P. G. Morris and R. E. Coupland
- Radiation response of mice maintained on a defined diet.
  Shirley Lehnert

Correspondence. 925
- Repression of the medical profession in Argentina.
  A. Campbell
- Radiation exposure to the patient in computerized tomography.
  P. Hobday and R. P. Parker

(Continued, inside back cover)

Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0007-1285
12632

18.5.79

December 1978

THE BRITISH JOURNAL OF RADIOLOGY

X-ray diagnosis

Radiation oncology

Nuclear medicine

Ultrasound

Radiological physics

Radiobiology

Radiation protection

and related disciplines

Published by
The British Institute of Radiology

The British Journal of Radiology

FOUNDED 1896

The Editorial Committee consists of:

The Editors:

D. K. BEWLEY, M.A., PH.D. F. STARER, F.R.C.P., F.R.C.R.

The Deputy Editors:

B. T. HALE, M.B., CH.B., F.R.C.R., D.M.R.T. N. W. RAMSEY, PH.D., F.INST.P.

J. ROYLANCE, F.R.C.R.

and

The Associate Editors:

A. B. AYERS, M.D., D.M.R.D., F.R.C.R.
THELMA D. BATES, M.B., CH.B., F.R.C.R., D.C.R.A.
D. COSGROVE, M.A., B.M., B.CH., M.SC., M.R.C.P.
M. F. COTTRALL, B.A., M.SC., PH.D., F.INST.P.
R. DICK, M.B., B.S., M.R.A.C.R., F.R.C.R.
C. D. R. FLOWER, M.A., F.R.C.P.(C), F.R.C.R.
N. E. GILLIES, B.SC., PH.D.
J. A. GLEESON, M.B., F.R.C.P., F.R.C.R., D.M.R.D.
H. GRAVELLE, B.SC., M.B., CH.B., F.R.C.P.(E.), F.R.C.R., D.M.R.D.
J. L. HAYBITTLE, M.A., PH.D.
C. R. HILL, B.A., PH.D., D.SC., M.I.E.E., F.INST.P.
D. H. KEELING, M.A., M.SC., M.B.
I. KELSEY FRY, D.M., F.R.C.P., F.R.C.R.
B. KENDALL, F.R.C.P., F.R.C.R., D.M.R.D.
H. B. MEIRE, M.B., B.S., L.R.C.P., M.R.C.S., D.M.R.D., D.OBST., R.C.O.G., F.R.C.R.
J. T. PATTON, M.R.C.S., L.R.C.P., F.R.C.R.
O. C. A. SCOTT, M.D.
T. SHERWOOD, M.B., M.R.C.P., F.R.C.R., D.M.R.D.
N. VEALL, D.SC., F.INST.P.

The Associate Editors Overseas are:

P. ARMSTRONG, M.B., B.S., F.R.C.R., D.M.R.D. (U.S.A.)
B. J. CREMIN, F.R.A.C.R., F.R.C.R. (South Africa)
J. R. CUNNINGHAM, M.SC., PH.D. (Canada)
H. A. LUKE, F.R.C.R., F.R.A.C.R. (Australia)
G. P. G. SIM, M.B., F.R.C.R., M.R.C.A. (New Zealand)
R. W. STANFORD, M.A., F.INST.P. (Australia)

Managing Editor: MRS. LEE SURRY

Communications should be addressed to the Editors in accordance with the Instructions to Authors which are published in the January issue of the Journal in each year and copies of which may be obtained on application to the Managing Editor.

ADVERTISEMENTS: Communications regarding accounts should be addressed to the Institute. All other communications should be addressed to Miss Hilary Cook, Advertising Manager, The British Journal of Radiology, Advertisement Department, 24a Litchfield Street, London WC2H 9NX.

SUBSCRIPTIONS: All communications should be sent to The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG, England. Notification of change of address should include an old mailing label and the new address. Claims for missing copies can only be allowed if received within two months of normal delivery date.

ANNUAL SUBSCRIPTION: (post free, payable in advance) £40·00 per annum (monthly) (U.S.A. $79). Single copies: £4·00.

Second class postage paid at New York. Mailing agents: N.Y. Expediters of the Printed Word Ltd., 527 Madison Avenue, Suite 1217, New York, N.Y. 10022, U.S.A.

The British Institute of Radiology

Incorporated by Royal Charter
Founded 1897

32 WELBECK STREET, LONDON W1M 7PG
Telephone: 01–935 6237 and 01–935 6867. Cable Address: "Britology, London W.1."

President: W. M. ROSS, T.D., D.L., M.D., F.R.C.S., F.R.C.R.

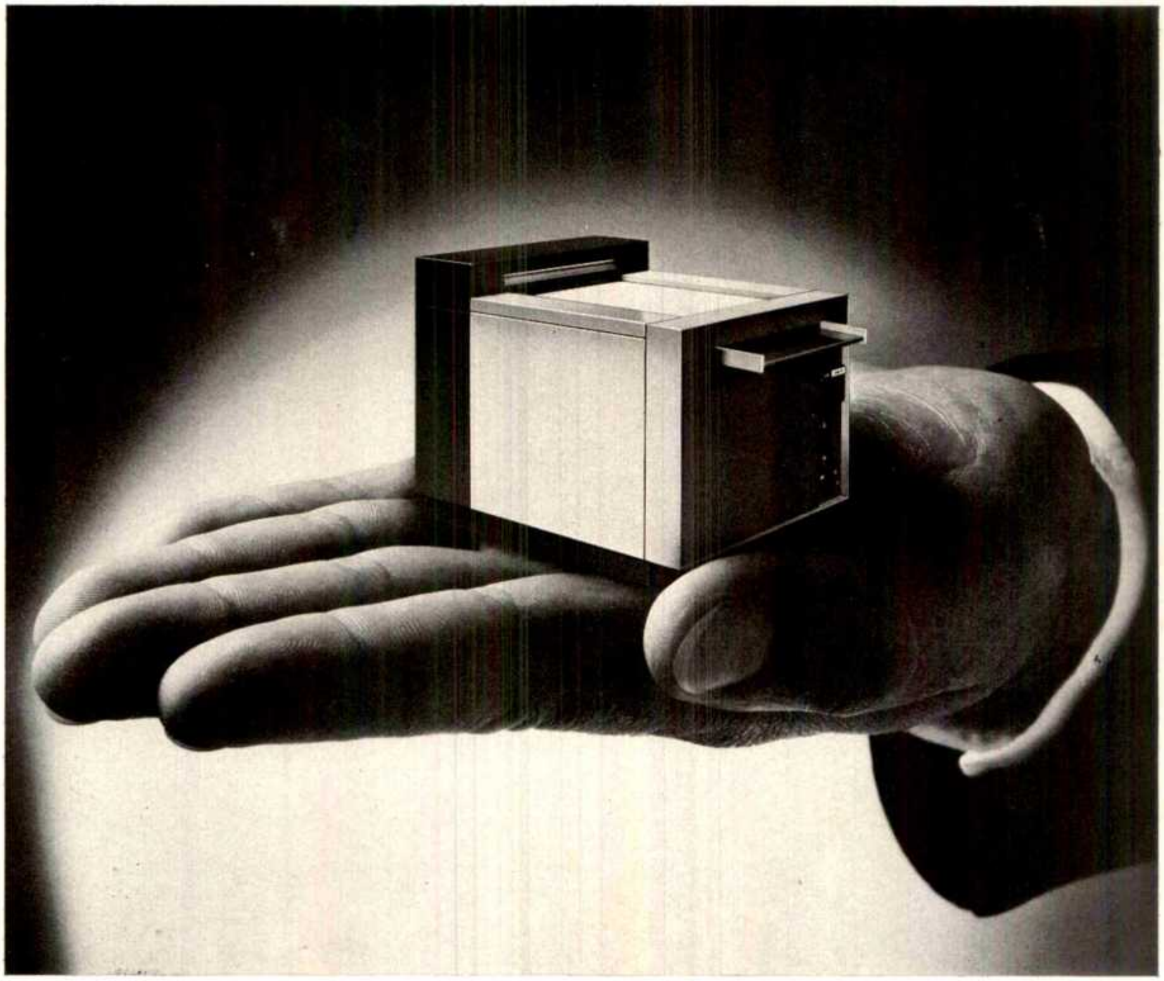
Hon. Secretaries:

W. HATELY, M.B., CH.B., F.R.C.P.E., F.R.C.R., D.M.R.D. S. B. FIELD, B.SC., PH.D.

Hon. Treasurer: D. T. KERRISK

THE BRITISH INSTITUTE OF RADIOLOGY is an association of persons interested in Radiology and allied subjects. Meetings are held monthly from October until May. Particulars of membership and other information may be obtained on application to the General Secretary at the Institute.

© British Institute of Radiology, 1978



The new CRONEX* T6 cuts x-ray film processing down to size.

High capacity x-ray film processing from a compact machine: that's the T6.
The CRONEX* T6 offers you the throughput you expect from far bigger processors and at a much lower cost. Easy to install and highly reliable, it is efficient and takes only 115 seconds for processing. In one hour you can process 175 35 x 43 cm films or 250 mixed sizes. The processor is compatible with the Du Pont Daylight System. Handles all CRONEX* medical x-ray films and is a perfect partner for our new CRONEX* automatic chemical mixer.

The T6 is silent when on stand-by and uses minimal amounts of electricity and water thanks to sophisticated solid state automatic controls with built-in logic.

The processor is designed to be installed in either conventional darkrooms or the most modern dispersed film handling areas, where its features permit a pleasant environment for staff and patients.

In addition, Du Pont's enthusiastic, experienced team of equipment service representatives stand behind all CRONEX* equipment: with friendly advice on layout planning, smooth installation, scheduled maintenance programmes and emergency assistance should it be required.

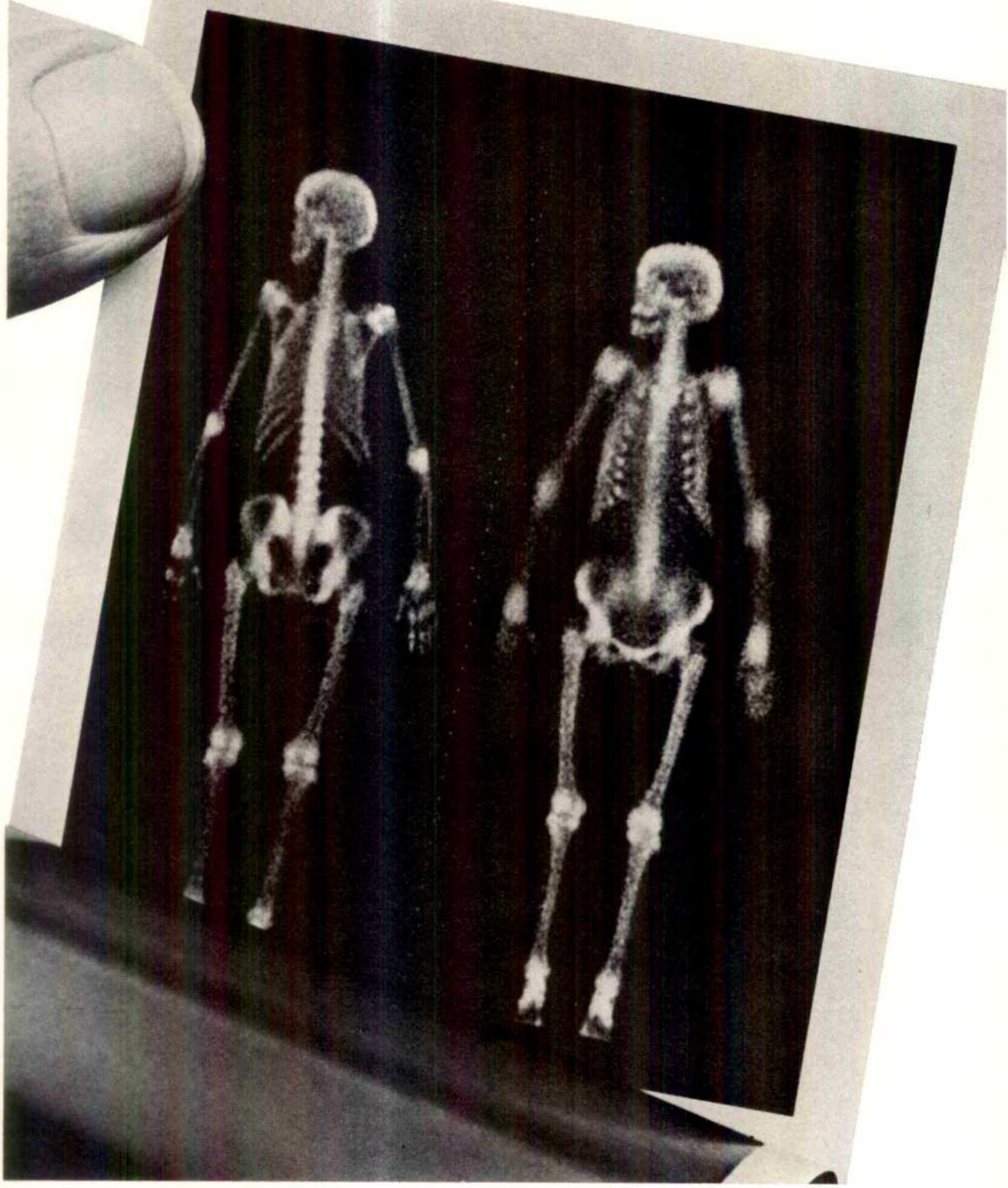
Save space. Save time. Save money. The T6 is one processor that really cuts film processing down to size. To find out more about the new CRONEX* T6, write to the address below.

CRONEX* T6. THE SMALL PROCESSOR WITH THE BIG CAPACITY.

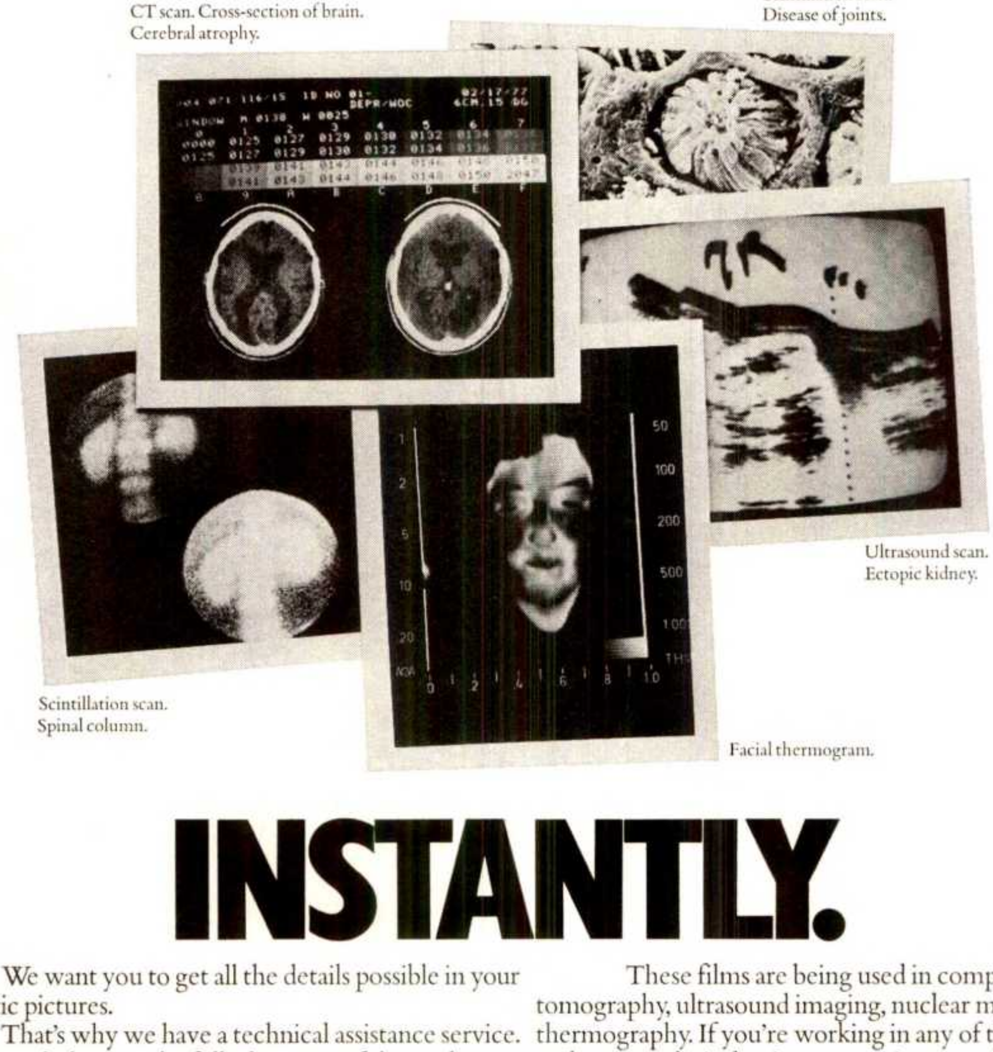
DU PONT

Du Pont de Nemours U.K. Limited – Photo Products Department – Hawkesden Road, St. Neots, Huntington, Cambridgeshire PE19 1QS
Tel.: (0480) 75341/(01) 2355286-88 Telex: 32159. *Du Ponts trademark

WE'LL HELP YOU GE



T THE INSIDE STORY.



CT scan. Cross-section of brain.
Cerebral atrophy.

Scintillation scan.
Disease of joints.

Ultrasound scan.
Ectopic kidney.

Scintillation scan.
Spinal column.

Facial thermogram.

INSTANTLY.

We want you to get all the details possible in your iagnostic pictures.

That's why we have a technical assistance service. Ve'd like to help you take full advantage of the quality e've built into all our professional instant films.

And since the picture can't be better than the nage on your video monitor, our experts are prepared to elp you achieve optimum results from your particular iagnostic equipment.

Polaroid black and white Land films have the ensitivity, resolution, exposure latitude and grey scale apability necessary to give you excellent diagnostic hotographs on the spot. One of our films will give you oth a positive and a negative instantly. With our olacolor 2 film you can record high-resolution colour nages in 60 seconds. All of our films are self-developing. ou don't need a darkroom or processing equipment to et the pictures you want.

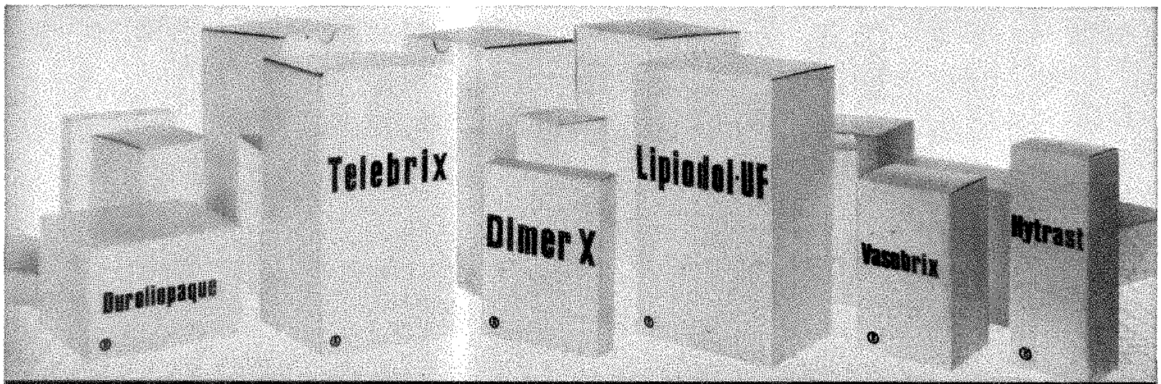
These films are being used in computerised tomography, ultrasound imaging, nuclear medicine and thermography. If you're working in any of these fields, make our technical assistance service part of your diagnostic system. It costs you nothing.

For more information or a demonstration, phone Ray Taylor on Freefone 2143 or write to Polaroid (U.K.) Ltd., Business and Professional Products Division, Ashley Road, St. Albans, Herts., AL1 5PR.

We can't help you diagnose your patients' troubles, but we can certainly help you diagnose your photography.

POLAROID
INSTANT FILMS FOR CRT RECORDING

'Polaroid' and 'Polacolor' are registered trademarks of Polaroid Corporation, Cambridge, Mass., U.S.A.
Polaroid (U.K.) Ltd., Ashley Road, St. Albans, Herts. ©Polaroid Corporation 1978



WE MANUFACTURE

contrast

MEDIA

OUR

products

ARE

known

WORLD-WIDE

OUR

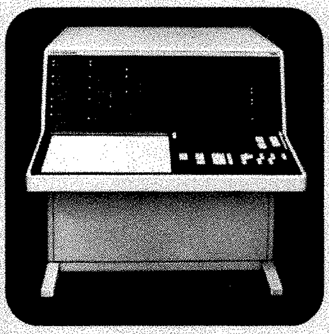
name isn't

GUERBET

BETTER CONTRAST MEDIA THROUGH RESEARCH

Laboratoire Guerbet, 16/24, rue Jean-Chaptal
93601 AULNAY-SOUS-BOIS Cedex - FRANCE
Telex : Guerbet 690682

TPS extended to Brachytherapy



Next to the highly accurate teletherapy programme the TPS offers more. It also provides extensive facilities for calculation of brachytherapy plans with needles, straight and curved wires and seeds.
The 'question and answer' mode of operation makes processing easy and virtually self-explanatory.
From the many applicational advantages we just mention:
- correction for tissue absorption
- correction for oblique filtration
- automatic source decay correction
- inherent self-checking on accuracy of source positions and dimensions
- dose information geometrically related to an anatomically recognisable point

This facility is now standard on all TPS equipment.

PHILIPS

N.V. Philips' Gloeilampenfabrieken
PCP/Medical Systems Division
Building QM, Eindhoven, The Netherlands

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd.
45 Nightingale Lane, London SW12 8SX

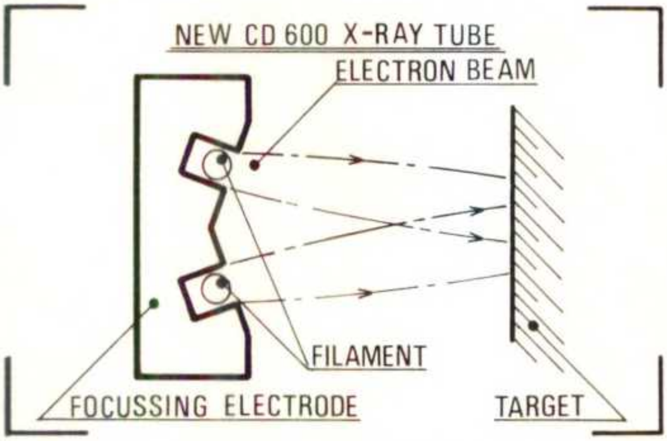
Medical Systems

NEW second generation

600 m Ap

Capacitor Discharge Mobile

- SUPER OUTPUT 600 mAp/125 kVp
- MILLISECOND SWITCHING 2–60 mAs in 15 steps
- IMPROVED MANOEUVRABILITY three forward speeds and two reverse – extra low speed for bedside adjustment
- UNIQUE HIGH POWER CD600 X-RAY TUBE fine focus, high capacity
- LOW COST half cost of cordless systems



The second generation series CD600 capacitor discharge X-ray tubes have been designed on a new principle using a focussing electrode to cut-off the tube current in place of the grid which was previously used.

With this tube, two 0·8 mm focal spots are superimposed on the target slightly shifted from each other. This results in a high power peak intensity distribution over a focal spot effective size 1·2×1·2 mm.

A great improvement is achieved in the Modulation Transfer Function over the conventional tube and therefore excellent detail at high tube mA loadings is achieved.

The use of this double focus combination also reduces individual filament temperature and provides longer tube filament life than conventional tube design.

Before making any decisions, contact us and arrange a demonstration in your own Department.

TODD RESEARCH LTD
ROBJOHNS ROAD
CHELMSFORD CMI 3DP
TEL. (0245) 62233/7 TELEX 99327

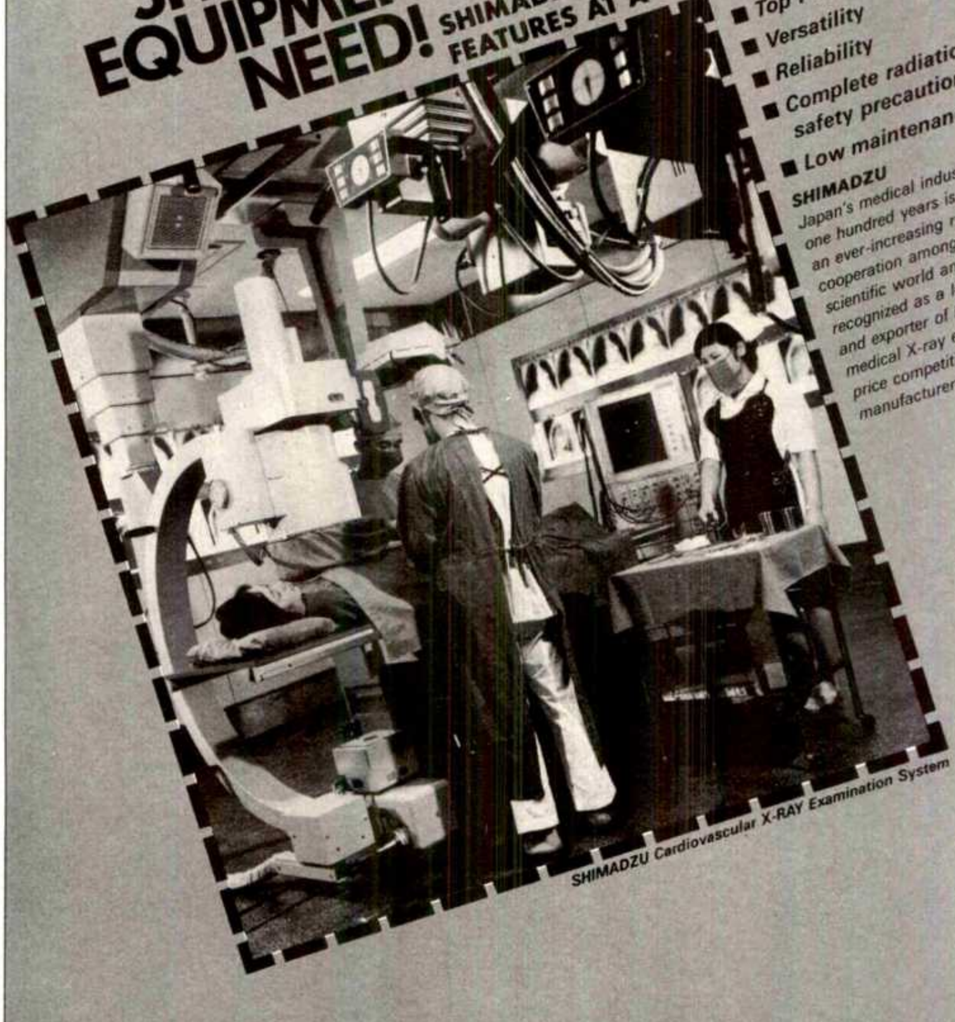
*Our 1978–9 catalogue is now available. Contact us and a copy will be mailed by return.

A ROOM FULL OF SHIMADZU X-RAY EQUIPMENT IS ALL YOU NEED!

SHIMADZU X-RAY EQUIPMENT OFFERS ALL THESE FEATURES AT A COMPETITIVE PRICE

- Top Performance
- Versatility
- Reliability
- Complete radiation safety precautions
- Low maintenance cost

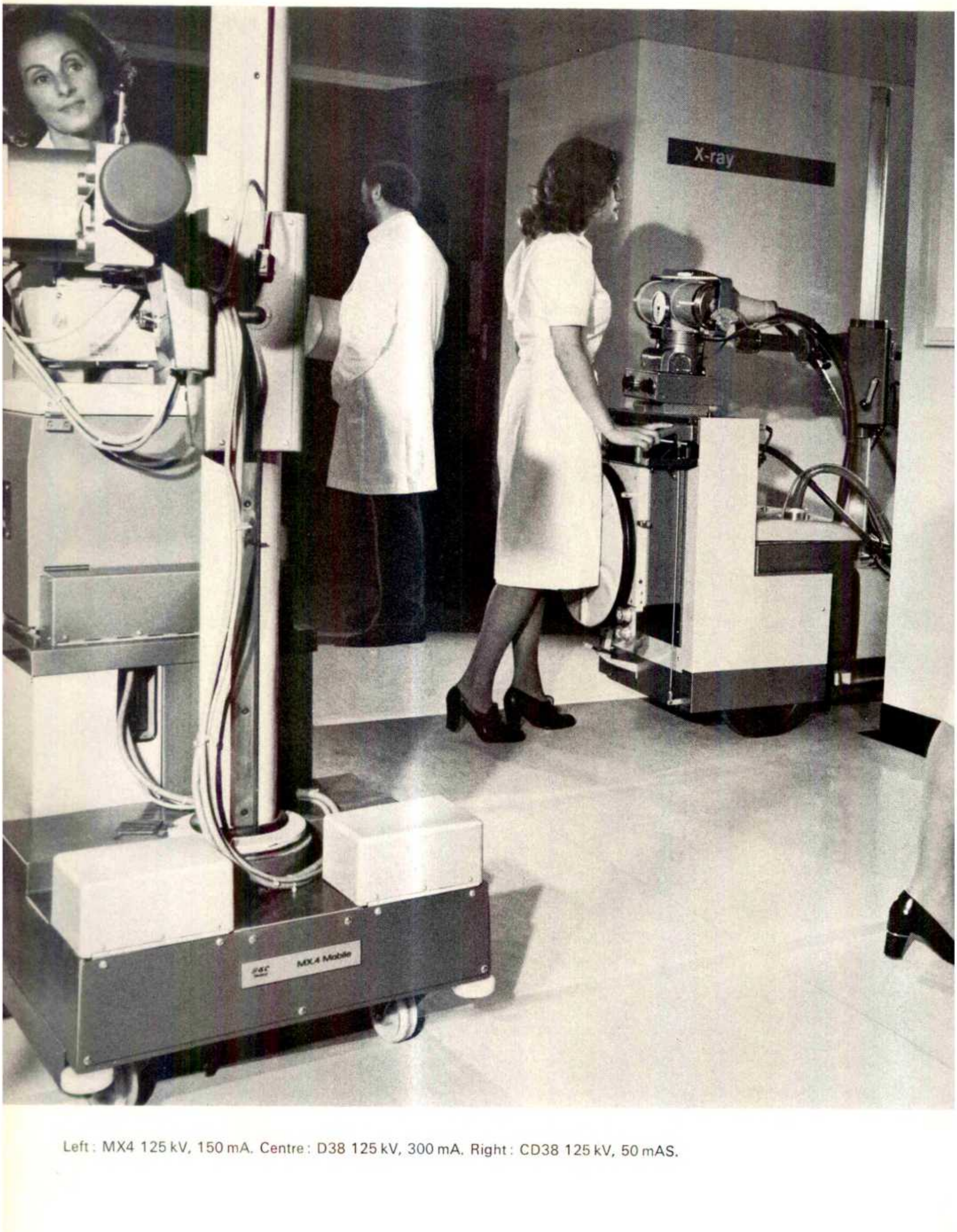
SHIMADZU
Japan's medical industry pioneer for one hundred years is continuing to play an ever-increasing role in international cooperation amongst the leaders of the scientific world and is internationally recognized as a leading manufacturer and exporter of highly sophisticated medical X-ray equipment at a price competitive with all leading manufacturers.



SHIMADZU Cardiovascular X-RAY Examination System

SHIMADZU
SEISAKUSHO LTD. KYOTO JAPAN
INTERNATIONAL MARKETING DIV.
14-5, Uchikanda 1-chome Chiyoda-ku, Tokyo Japan Phone: Tokyo 03-296-2352
Overseas Telex: No.0222-4275 SHMDT J. Cable Address: SHIMADZU TOKYO

SHIMADZU MID-EAST SCIENTIFIC OFFICE
Flat No. 10, 16 Mahmud Azmi Street Zamalek, Cairo
Arab Republic of Egypt(P.O. Box: Zamalek P.O. Box 32, Cairo)
Phone: 804375 Cable Address: MIDSHIMAZU, CAIRO



Left: MX4 125 kV, 150 mA. Centre: D38 125 kV, 300 mA. Right: CD38 125 kV, 50 mAS.

Take a closer look

The relationship of engineering quality with practical hospital workload is never more stringently tested than with Mobile X-ray Equipment.

The MX4 Mobile
is based on a monoblock tubehead design with medium power output. A rugged and compact mobile unit with practical economy in mind.

The high output D38
has forged its own special reputation with radiographers internationally – their comments and co-operation have refined its character and performance over many years. A superbly rugged, very mobile system with high output X-ray factors.

The new Capacitor Discharge System CD38
inherits all the proven mechanical features of the D38. Engineered in combination with a capacitor discharge X-ray generator to give consistently stable radiographic performance and high output even from low capacity mains supplies.

For further information contact Mike Bench on 01-904 1288.

GEC

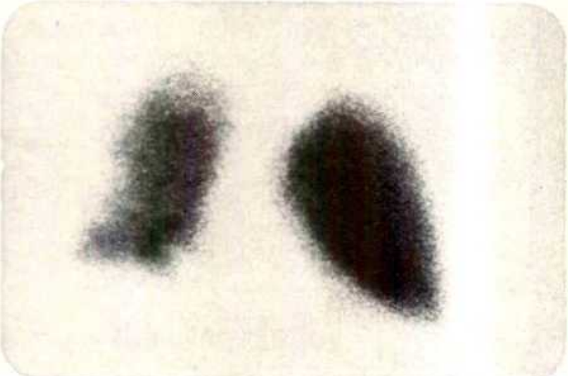
Medical

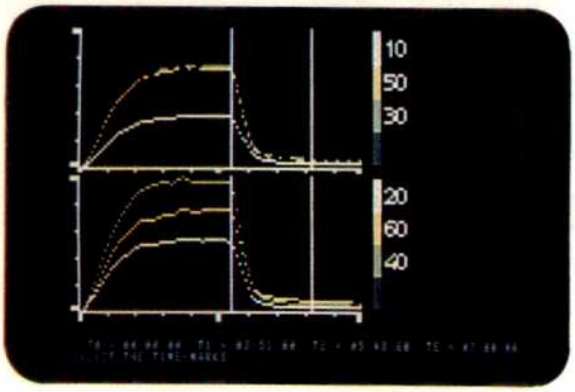
Responsible technology

GEC MEDICAL EQUIPMENT LIMITED · P.O. BOX 2 · EAST LANE · WEMBLEY · MIDDLESEX HA9 7PR · ENGLAND
TELEPHONE: 01-904 1288 · TELEX: 922177 · CABLES: SKIAGRAM, WEMBLEY

Conclusive evidence

78-01-02 LUNGVENTILATION DORSAL, 125 XE, TRANSIT TIME
0 -100% M=54 N=31094 T=01:00.00



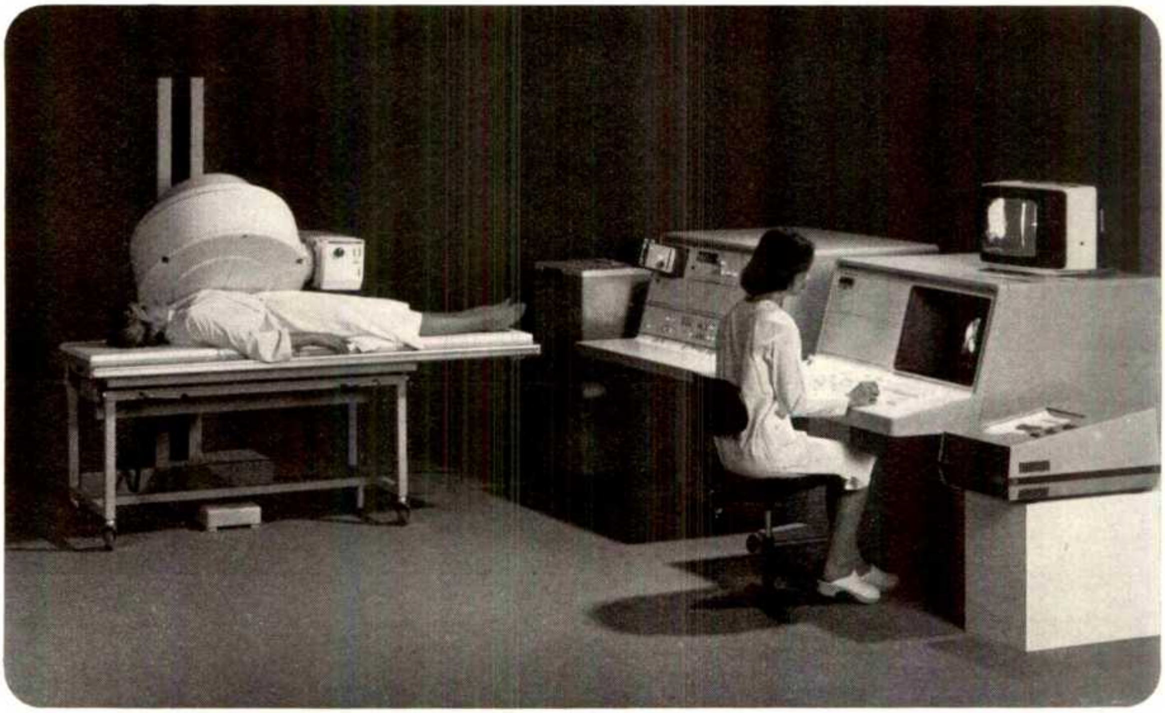


Medical Systems

The Philips Large Field Gamma Camera, with its full 38 cm field of view, provides high-resolution images with excellent homogeneity. The dorsal view of two lungs on a single image, shown in black and white on the left, is a typical example.

The colour image and curves, forming part of a lung ventilation study, have been obtained using the Philips Processing and Display System. This system offers a full range of programs for functional dynamic studies such as those of the heart, kidneys, lungs and brain. The programs, proved in clinical practice, are fast and easy to use, offering a wealth of diagnostic information.

Together, the Large Field Gamma Camera and the Processing and Display System provide conclusive evidence in doubtful cases.



The **Large Field Gamma Camera,** with its **full** 38 cm field of view, offers superb imaging facilities.
The imaging system, based on the Anger principle, consists of 37 bialkali detectors arranged on a single 48 cm diameter crystal. Resolution and homogeneity are excellent, and high count rates can be accepted without significant distortion. Features of the Large Field Gamma Camera include:

- high resolution with excellent homogeneity (3 mm intrinsic lead bar resolution)
- high count rate (100 K counts/s), ^{99m}Tc, 20% window
- fast, easy operation
- extremely stable electronics
- separate scopes for positioning and recording
- full range of ancillary equipment

The **Processing and Display System** provides a wide choice of data acquisition and processing programs for static and dynamic studies. Its functions include quantitative and qualitative analysis, correction of image information, enhancement of selected spatial frequencies, and functional scanning. The results are displayed as enhanced images, time/count histograms, and alphanumerical information including analysis functions and lists of patients.
Data processing and data acquisition, even from several cameras, can take place simultaneously, allowing a large work load to be handled.

In addition to the Large Field Gamma Camera and the Processing and Display System, Philips offer a **Normal Field Gamma Camera** with a 26 cm field of view, as well as a complete range of peripherals.
Multi Formatter. For direct recording of static, dynamic, whole body and gated studies on standard X-ray film.
Total Body Scan Unit. For large-area scanning in combination with the Multi Formatter. **Spectrum Analyser.** For display of the radio-isotope spectrum, and window settings.

Part of a complete program of nuclear medicine equipment and systems, and fully supported by an international service organization, the Philips Large Field Gamma Camera and Processing and Display System combine operational simplicity and efficiency with applicational flexibility and reliability.

COUPON

If you would like further evidence on our nuclear medicine program, complete this coupon and send it to: Philips Industries, Medical Systems Division, Building QM, Room 347, Eindhoven, the Netherlands

Institution: ____
Name/Position: ____
City/Country: ____
Street/P.O. Box: ____

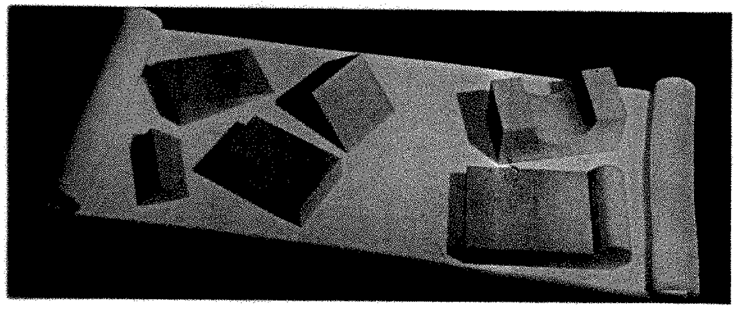
PHILIPS

Philips Medical Systems
A Division of Philips Electronic and Associated Industries Ltd.
45 Nightingale Lane London SW12 8SX

polyfoam®

ANSAFONE SERVICE
operates 5pm-9am
and at weekends

unique padding permits passage of X-rays without showing on the plate



A typical example of the use of Polyfoam is the provision of a warm and comfortble cover for an X-ray couch, thus saving patients from having to endure a hard, cold surface when being X-rayed.

For further information write or telephone.

HINDERS-LESLIES LIMITED
Higham Hill Road · London · E17 6EJ
Telephone: 01-531 7172 (10 lines) plus Ansafone

progress
through
research

Member of the SMITH & NEPHEW Group of Companies

THE UNIVERSITY HOSPITAL OF AMSTERDAM

HOLLAND

including the hospitals
BINNENGASTHUIS WILHELMINA GASTHUIS

wholetime diagnostic radiologist

Applications are invited from suitably qualified full-time Diagnostic Radiologists to join the Staff of the Department of Radiology.

The appointee will be expected to take part in the teaching programme and ample facilities for participation in research projects are available.

The commencing salary according to qualifications and experience will be within the range of Dfl. 90.228,– to Dfl. 118.368,– per annum supplemented by a holiday allowance of 8%.

Further particulars may be obtained from Professor Dr. D. Westra or Professor Dr. F.L.M. Peeters, telephone 010 31 20 578 2125 or 2316 respectively (direct extension dial).

Applications in writing with curriculum vitae to be submitted to Head of Personnel Department, Eerste Helmersstraat 104, 1054 EG Amsterdam, Holland.

AXISCAN 5

The new portable real~time ultrasound scanner from Kontron Roche

• Built to a unique design, offering all the facilities you require for obstetric and general abdominal scanning • Truly portable design makes it very easy to use in ante-natal clinics and other departments within hospitals • Simple operation facilitates routine obstetric investigations with the minimum of fuss • Fetal maturity estimations can be established quickly using the integral electronic calipers which automatically reproduce an on-screen digital display. • Results are permanently recorded with the built-in camera. • The excellent grey-scale display shows moving structures up to 25 cm deep. • All our customers are backed by a national 24 hour Kontron Roche service.

KONTRON ROCHE

serving hospitals throughout the world

For further information, please complete the coupon below and post to Kontron Instruments Limited, PO Box 88, St. Albans AL1 5JG, or telephone St. Albans (0727) 33221.

Please contact me to arrange a demonstration of/send me further information about/ the Axiscan 5.

NAME. . . . .

POSITION . . . .

ADDRESS. . . . .

. . . .

. . . .

TELEPHONE . . . .

University of London
Royal Postgraduate Medical School

FAST NEUTRON THERAPY

9–12 April 1979

Three similar courses have been organised by the Royal Postgraduate Medical School and the Medical Research Council Cyclotron Unit, Hammersmith Hospital, and have been found to be particularly valuable to doctors interested in treating patients with high LET radiation and, in particular, for those who have already started fast neutron programmes or will start them in the near future.

The fourth course will be held from 9 to 12 April 1979 and will consist of:

Lectures and discussions on the physical, biological and clinical effects of 7.5 MeV neutrons. Clinical effects on tumours and normal structures will be compared with those produced by photons.

The demonstration of patients treated with fast neutrons during the past nine years.

Practical demonstrations and explanations of the special techniques which have been evolved.

Demonstrations and treatment of patients actually receiving neutron radiation at the time of the course.

Throughout the four days of the course, members of the Fast Neutron Clinic, radiobiologists, physicists, engineers and the MRC isotope staff will be available for discussion with the participants.

Because of the emphasis on the demonstration of patients the number of clinical participants must be restricted to a maximum of fourteen. In addition, ten physicists could be included for lectures and demonstrations, excluding the clinical demonstrations.

Course organiser: Dr. Mary Catterall

Course fee: £100 (full course, including catering)
£80 (excluding clinical demonstrations, including catering)

Application forms may be obtained from:
The School Office (SSC)
Royal Postgraduate Medical School
Hammersmith Hospital
Du Cane Road, London W12 0HS
Telephone: 01–743 2030 ext 351

Closing date for applications: 1 February 1979

STAFF RADIOLOGIST

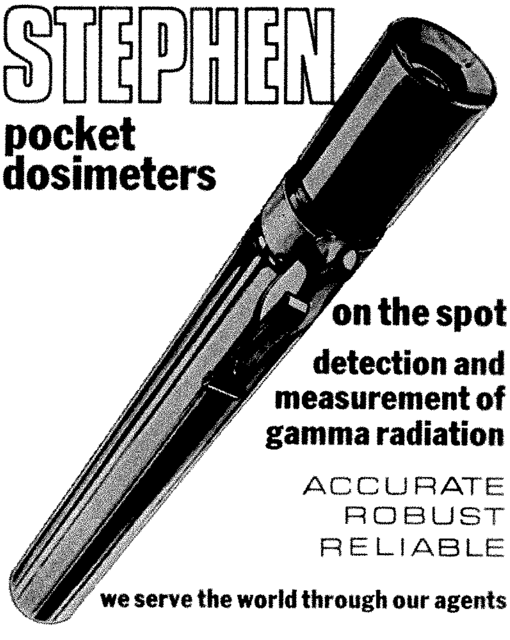
Royal Alexandra Hospital for Children
Camperdown (Sydney), N.S.W., 2050.
Australia

Applications are invited from qualified diagnostic radiologists for appointment to the above full-time position in this 500-bed paediatric teaching hospital of the University of Sydney. The Department of Radiology has entered into a major re-equipment programme which is nearing completion. Experience in C.T. Scanning, Ultrasound and Angiography would be an advantage. Other staff members are the Director and one full-time radiologist plus a small number of visiting staff.

Salary in the range $A24,762/$A30,719 per annum with a limited right of private practice within the Health Commission Private Practice Scheme.

Additional information may be obtained from Dr. M. de Silva, Director of Radiology. Applications with curriculum vitae and the names of not less than two referees to J. S. Yu, General Superintendent.

STEPHEN
pocket dosimeters



on the spot detection and measurement of gamma radiation

ACCURATE
ROBUST
RELIABLE

we serve the world through our agents

R·A·Stephen
AND COMPANY LIMITED
Miles Road Mitcham CR4 3YP Tel 01-648 1668/9

New from BDH.

Uromiro-an important advance in contrast media.

Uromiro (iodamide) is a new salt with important advantages in urography and angiography.[1]

In urography Uromiro combines lower levels of diuresis[2] with active tubular secretion[3] resulting in excellent nephrographic and pyelographic phases.

Uromiro is also well tolerated in a wide range of doses in abdominal and peripheral angiography with minimal and transient side effects[4].

Uromiro-clear new benefits for the radiologist from BDH Pharmaceuticals.

References 1. Bonati et al, (1965) Arzneimittel-Forschung, 15, 222-229. 2. Bellizi, (1966) Radiologica Radioterapia and Fisica Medica, 21, 3. 3. Bollerup et al, (1975) European Journal of Clinical Pharmacology, 9, 63-67 4. Kaude, (1973) Der Radiologe, 13, 271-275

BDH Pharmaceuticals Ltd, Lenten House, Lenten Street, Alton, Hampshire GU34 1JD. Telephone Alton (0420) 88767. Telex 858435. Uromiro and BDH are trade marks.

SONARSTAT
ULTRASONIC COUPLANT

SONARSTAT is a new Medical Ultrasonic Couplant featuring a unique glycerol/glycol base designed to optimize both ultrasonic energy transfer and acoustic impedance.

SONARSTAT will improve the quality of your medical ultrasonics while providing patient protection.

Available in 12 oz. dispensers and gallons, SONARSTAT is less expensive than the thickened water gels offered by competitors.

Request our **FREE SAMPLE 12 OZ. DISPENSER** along with complete technical data and pricing.

DIAGNOSTIC SONAR LTD
"The Couplant People"

1 Grange Road,
Houstoun Industrial Estate,
Livingston EH54 5DE.
Tel. 0589 35165/6

Made under licence from Echo Laboritories, Pennsylvania, USA.

COPY DATE CHANGE

Will advertisers please note the following copy date change.

February issue Wednesday 20 December

Please ensure all copy reaches the Advertisement Department, 24a Litchfield Street, London WC2 9NX by this date.

TECHNICAL CONSULTANT—EUROPE

Leading U.S.A. manufacturer of X-ray contrast media and accessories seeks Technical Consultant to liaise with dealers and Radiologists in Europe. Continental language speaker required. Substantial travel from home base is envisaged. A liberal salary and expenses and excellent prospects will be available to the successful applicant, who must be a qualified Radiologist or have previous X-ray marketing experience. Replies with salary required to Box no. 15, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

British Journal of Radiology

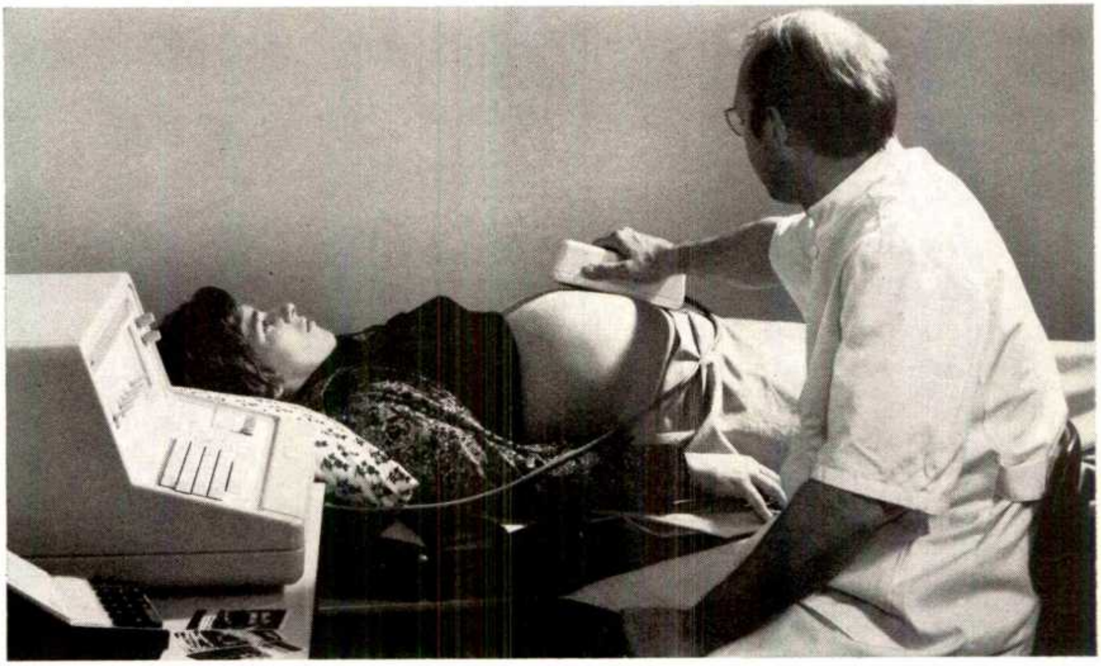
TEACHING BOOKLETS

No. 1 *The Physical Aspects of Radioisotopic Organ Imaging,* by K. G. Leach (1976)	£1·50
No. 2 *Introduction to the Principles of Diagnostic Ultrasound,* by H. B. Meire and P. Armstrong (1976)	£1·40
No. 3 *Fundamental Aspects of Medical Thermography,* by W. M. Park and B. L. Reece (1976)	£3·40

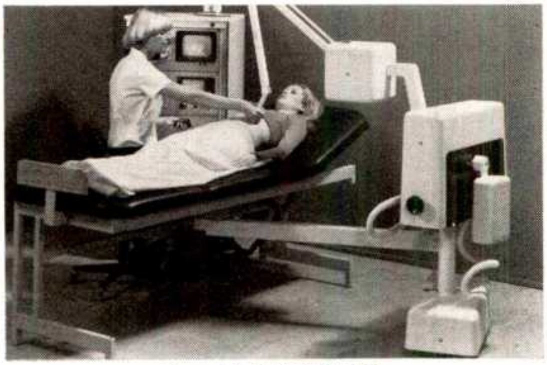
Available from the Publications Office,
British Institute of Radiology,
32 Welbeck Street, London W1M 7PG

The ultrasonic challenge accepted

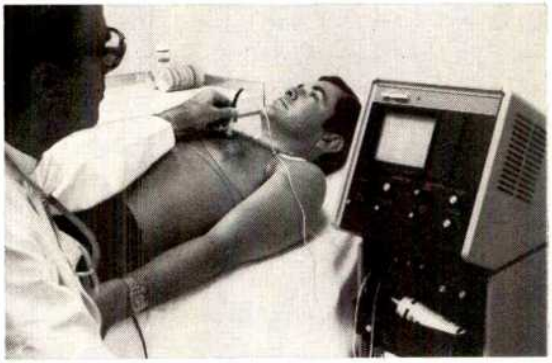
– NOW ALSO IN ECHOCARDIOGRAPHY



Sono DIAGNOST R
For real-time imaging particularly in obstetrics and gynaecology



Sono DIAGNOST B50
For tomographic imaging in B-mode, with A-mode
and M-mode facilities



Sono DIAGNOST M
For echocardiography in T.P. mode

Sono DIAGNOST A (not illustrated)
For echo-encephalography in A-scan mode

For details please contact Philips Medical Systems, Ultrasonics Division,
45 Nightingale Lane, London SW12 8SX. Telephone: 01-673 7766.

PHILIPS

PHILIPS **Medical Systems**

Your Scintigraphy Kit

Your kit starts with any of our three simple one-step preparations which combined with our new Sterile Technetium-99m Generator offers a complete package for liver, lung, bone and brain scintigraphy. Later we will be adding more kits to our range.

All our kits are tested extensively in clinical trials which include the use of other technetium-99m generators as well as our own. All are terminally sterilized and every batch is animal tested.

Agent for Bone Scintigraphy

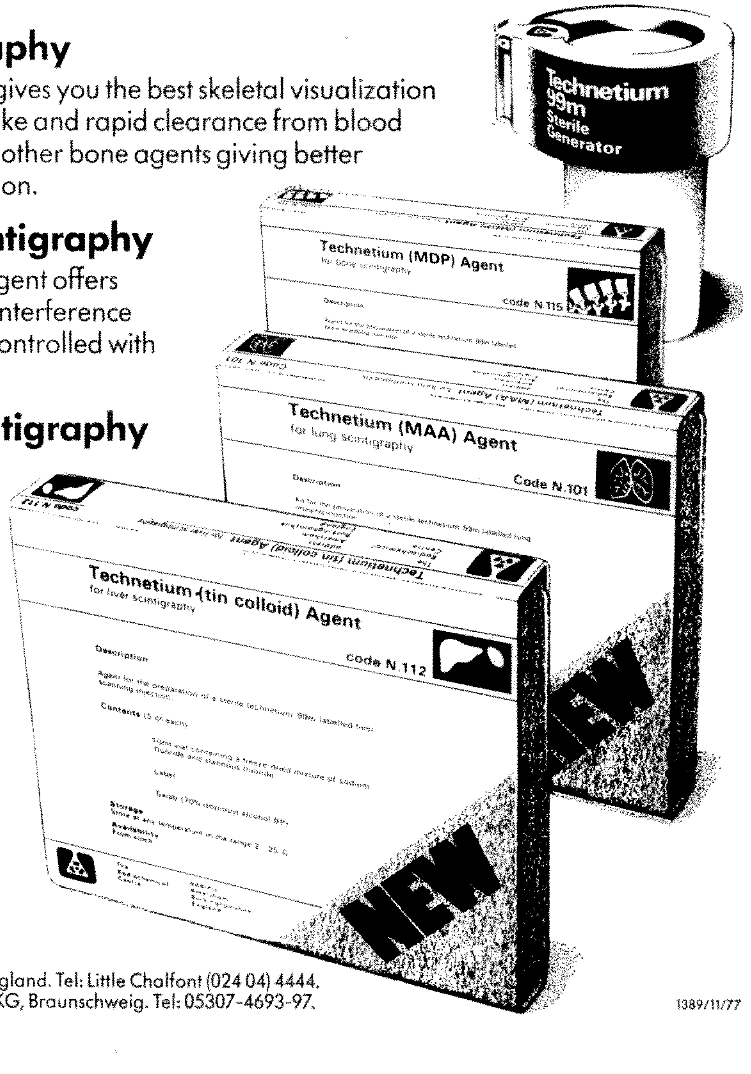
Our Technetium (MDP) Agent gives you the best skeletal visualization available today. The high bone uptake and rapid clearance from blood and soft tissue makes this superior to other bone agents giving better definition and improved discrimination.

New Agent for Lung Scintigraphy

Our new Technetium (MAA) Agent offers detailed lung visualization, with no interference from the liver. Particle size is strictly controlled with the majority in the range of 10–80μ.

New Agent for Liver Scintigraphy

The latest addition to our range is the unique Technetium (tin colloid) Agent. Its preparation is much simpler than sulphur colloid agents and requires no heating stage. It will visualize liver and spleen and unlike agents based on phytate, the colloid is formed in the vial, allowing quality control checks prior to injection.



**The Radiochemical Centre
Amersham**

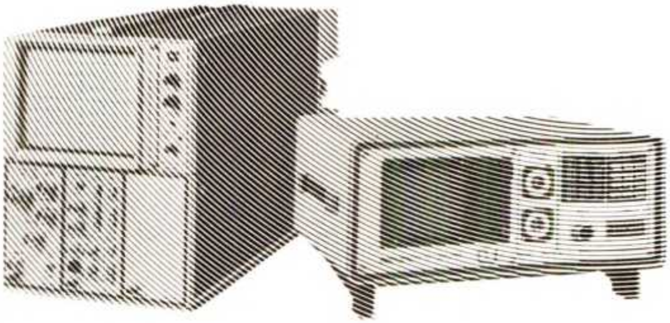
The Radiochemical Centre Limited, Amersham, England. Tel: Little Chalfont (024 04) 4444.
In W. Germany: Amersham Buchler GmbH & Co, KG, Braunschweig. Tel: 05307-4693-97.

1389/11/77

40 years of experience and expert knowledge can be made yours very easily

Oldelft

Oldelft England Ltd
16 Barclay Road, Croydon CRO 1JN
Tel. (01) 681 1171, telex 946154



The completest range of ultrasound equipment: gray-scale scanners, motorized arc scanners, linear phased array real time scanners, sector phased array real time scanners, M-mode monitors and all accessories for recording data on line-scans or video systems.
This Toshiba ultrasound equipment is characterized by unrivalled image definition, simplicity of operation and professional design.
It is sold and serviced by Oldelft throughout Europe.

Radiodiagnosis
Odelca x-ray cameras
100mm System for spotfilm photography
Deltorax chest film changer
Odelscope image intensifier for fluoroscopy

Ultrasound
Real time linear phased array systems
Cardiac phased array sector scanners
General purpose gray-scale compound scanners

Nuclear medicine
Gamma cameras with complete range of accessories (e.g. multi-imager, whole body scanning bed)

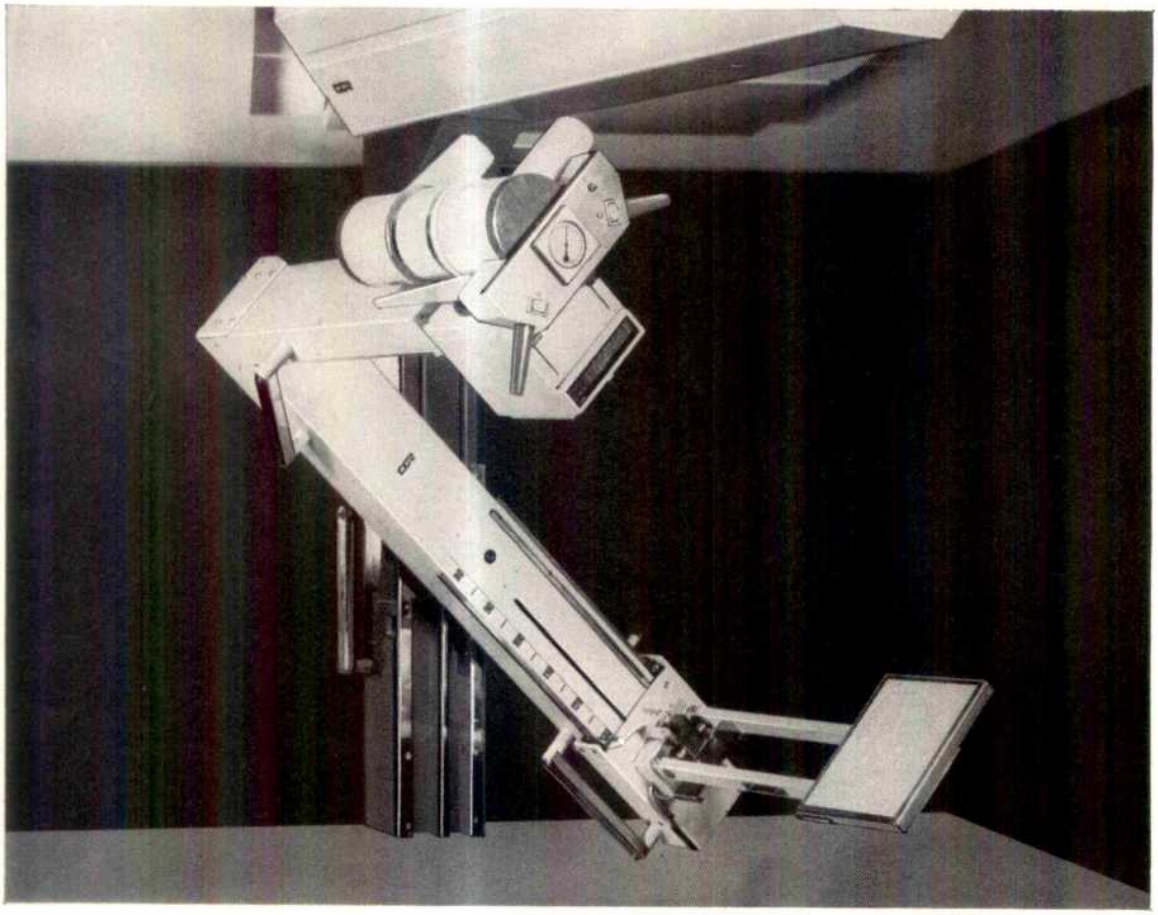
Radiotherapy
4 and 15 MeV linear accelerators
Cobalt units

Radiotherapy planning
Simulix-Y simulator with Simtomix accessory for analog whole body tomography

Pulmonary function testing
Computerized equipment for the pulmonary lab
Automated procedures in spirometry, flow/volume loop analysis and exercise testing

Head Office: Holland, Oldelft Deltronix bv, Den Haag Fruitweg 9, Tel. (070) 88 89 63
België/Belgique 2100 Deurne, Twee Gezusterslaan 34, Tel. (031) 24 93 05.
Deutschland D 6300 Giessen Lahn, Postfach 5420, Tel. (0641) 4 10 49.
España Madrid 16, Uruguay 13. Tel. (01) 259 1698.
France 91403 Orsay, B.P. 86, Tel. (01) 907 5900.
Italia 00146 Roma Via della Vasca Navale 84. Tel. (06) 55 84 311.
Sverige 17206 Sundbyberg 6 Postbox 670. Tel. (08) 98 38 95.
Schweiz 8618 Oetwill am See Zelglistrasse 5. Tel. (01) 92 91 318

Specifically for casualty
and
neuroradiology



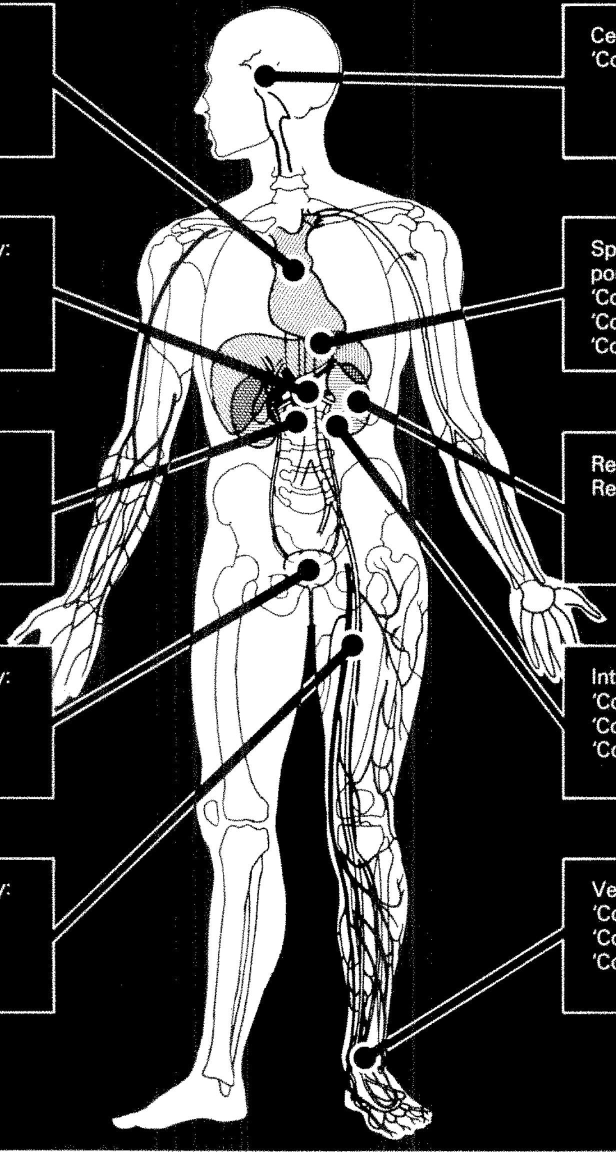
ARCO
UNIVERSAL
from
CGR

CGR now introduce the Arco Universal unit, the versatility of which is achieved by providing isocentric movements about a point in space. It is thus suitable for neuroradiology, general casualty and routine radiology with 360° tube rotation about a horizontal axis, 360° cassette rotation and wide vertical adjustment.

This general purpose installation produces an image quality as outstandingly high as specialised X-ray units. The quality, in fact, that is CGR.

Full details and specifications from
CGR MEDICAL LIMITED
Astronaut House, Feltham, Middx. Tel: 01-890 8166

The 'CONRAY' range of contrast media puts your patient fully in the picture



Angio-cardiography:
Cardio – 'Conray':
'Conray 420':
'Conray 280'

Abdominal-aortography:
'Conray 280':
'Conray 420':
'Conray 325':
Cardio – 'Conray'

Gastroenterography:
Gastro – 'Conray'

Retrograde cystography:
'Conray 280':
'Conray 420'
(suitably diluted)

Peripheral arteriography:
'Conray 280'

Cerebral angiography:
'Conray 280'

Splenography and portal venography:
'Conray 280':
'Conray 420':
'Conray 325'

Retrograde pyelography:
Retro – 'Conray'

Intravenous urography:
'Conray 325':
'Conray 420':
'Conray 280'

Venography:
'Conray 280':
'Conray 420':
'Conray 325'

Conray Contrast Media

There is a wide variety of formulations and almost certainly one to meet your specific requirements however exacting they may be.

'Conray'* contrast media are formulations of meglumine iothalamate, sodium iothalamate or combinations of the two.

Full information supplied on request to
May & Baker Ltd Dagenham Essex RM10 7XS
*trade mark of Mallinckrodt Inc.

M&B May&Baker

A member of the Rhône-Poulenc Group of Companies

MA 6535

GEVAERT AGFA-GEVAERT

Contrast, definition, brilliance- in a word, CURIX

Enquiries have proved that most radiologists working with Curix RP1 film prefer the material because of its outstanding qualities.

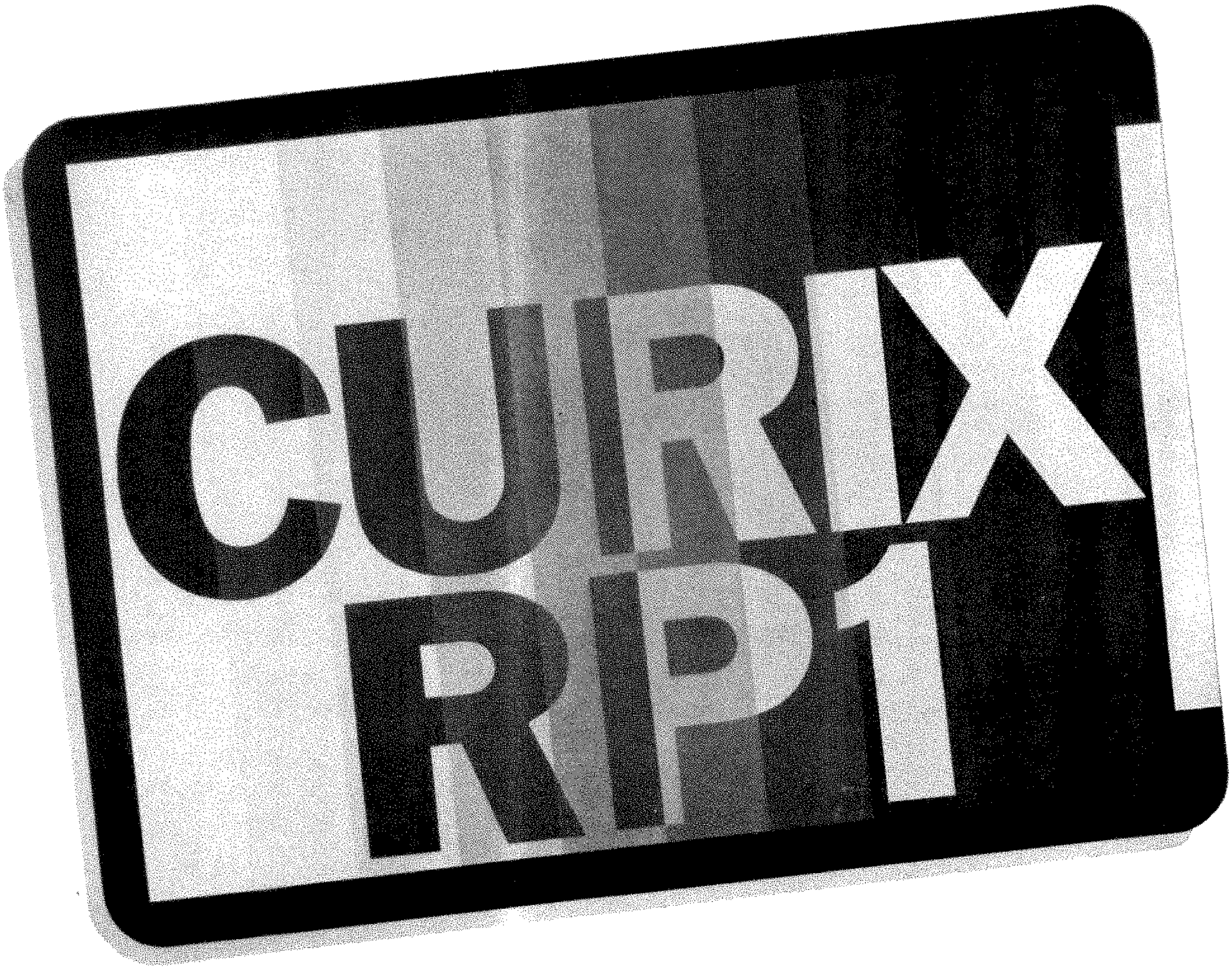
In making their choice, low fog level, contrast, image sharpness and sensitivity were of prime importance. In a word, they required "quality". Curix offers that quality.

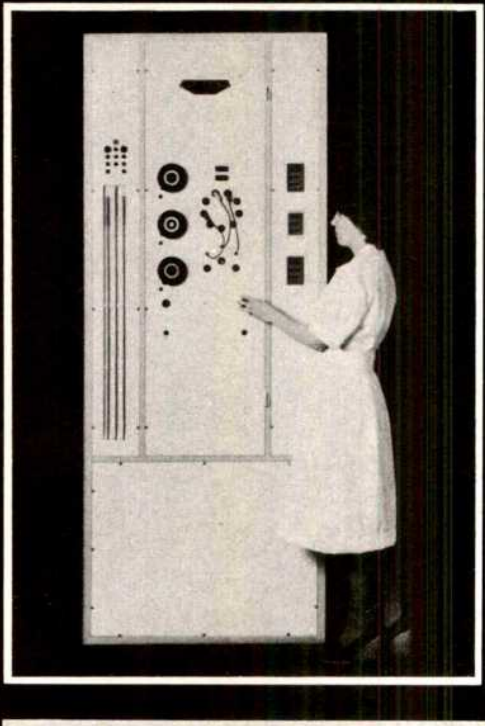
The film combines all the desired properties which give the radiologist more detailed information on which to base a safe, sure diagnosis.

It's easy to see why Curix is our biggest selling X-Ray film.

Isn't it time you proved the brilliance of Curix RP1.

Further information from:
Agfa-Gevaert Ltd.,
Medical X-Ray Sales Dept.,
27 Great West Road, Brentford,
Middlesex TW8 9AX.
Tel: 01-560 2131



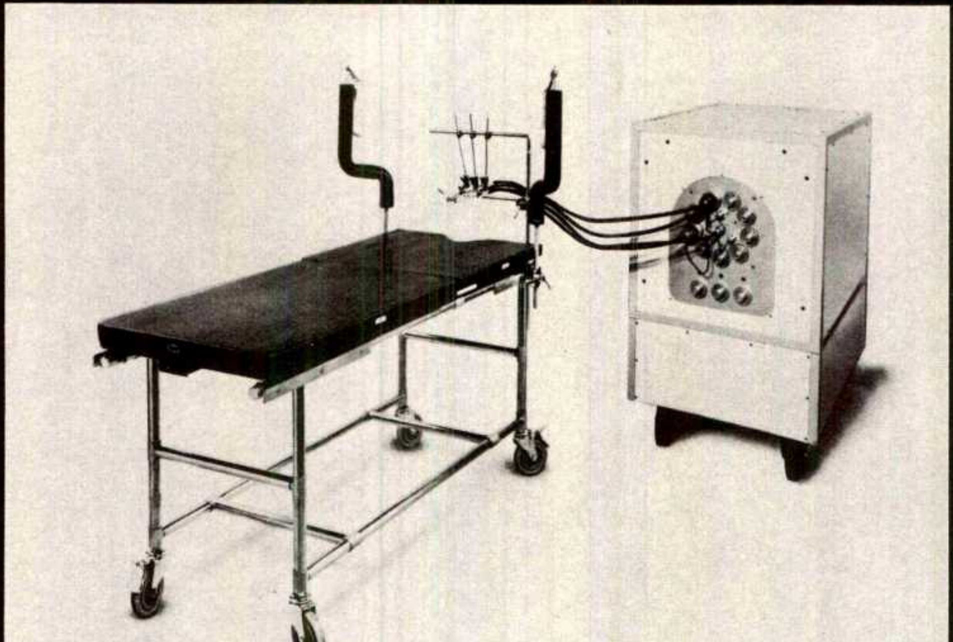


Cathetron
Remote loading Intracavitary unit using Cobalt 60.

The Cathetron has now been in clinical use for over a decade and is used by well over 30 hospitals in nearly 20 different countries.

Use of the Cathetron gives full protection, from radiation hazards, to all staff and reduces treatment time to minutes, thus ensuring that the Catheters stay in their correct location. These short treatment times mean that many patients can be treated as out-patients and therefore need not take up valuable bed space.

The Cathetron is used for surface mould treatments; treatments of the oesophagus and bronchi as well as gynaecological cases.



TEM Instruments Limited

Gatwick Road, Crawley, Sussex, RH10 2RG, England Tel 0293 31244
Telex 87397, Grams TESTMENT CRAWLEY

Paediatric patients range from new-born babies to full-grown adolescents.

That is why the DIAGNOST 73P dedicated paediatric system has been designed to cope with children from 0 to 90.

Based on the DIAGNOST 73 universal diagnostic system, the DIAGNOST 73P is provided with quick-change positioning supports for babies and young children, as well as a special support for urology.

In addition to its wide range of paediatric examinations, the DIAGNOST 73P converts in minutes to a versatile diagnostic system for examinations in older children and adults: there is n need to invest in a second stand for larger children and the DIAGNOST 73P offers full facilities for the busy general X-ray department.

PHILIPS

Write for further information to
Philips Medical Systems, Eindhoven, The Netherlands
or Philips Medical Systems, 45 Nightingale Lane, London SW12 8SX.

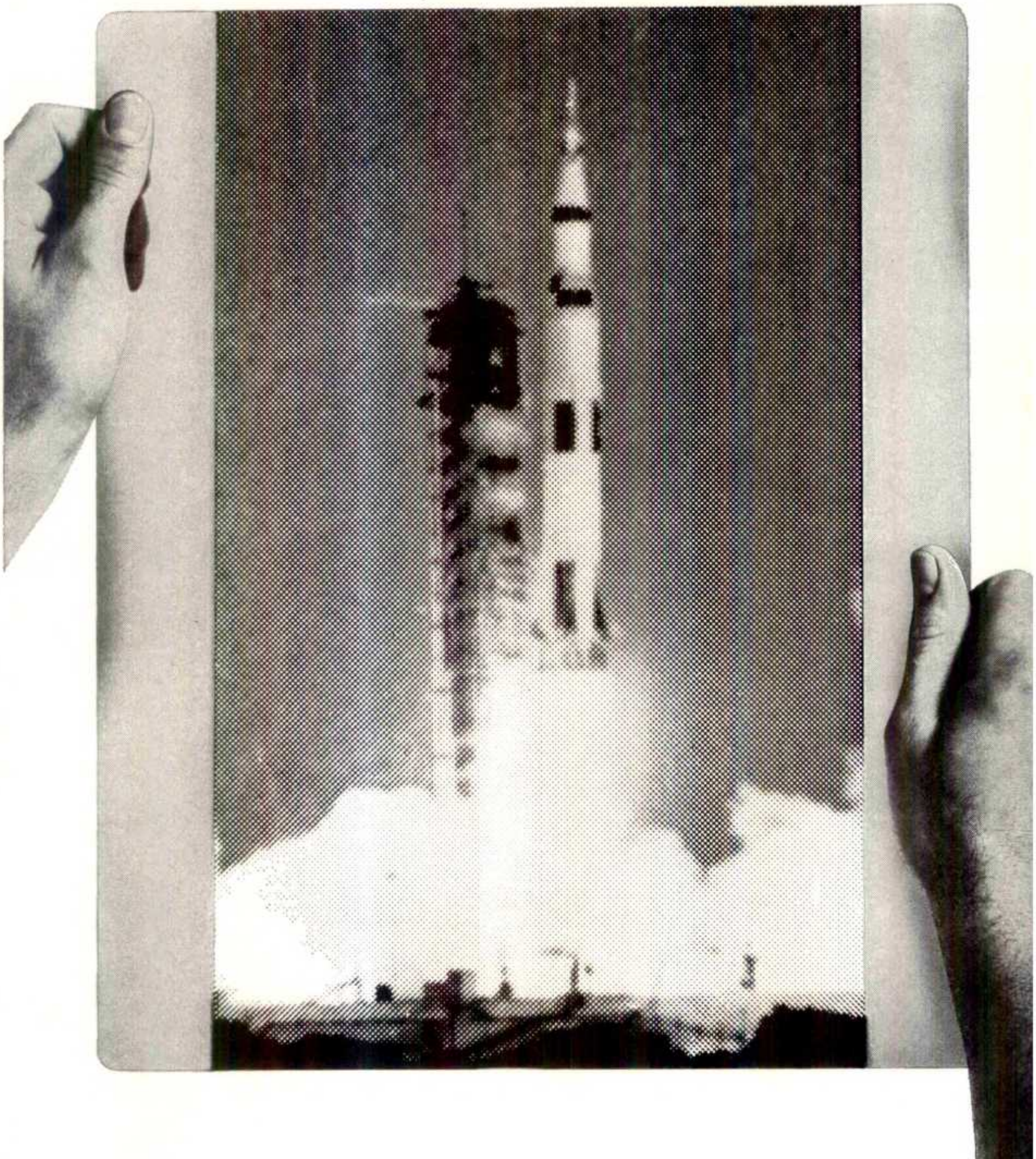
Medical Systems

Vidicam

The video hard copier

- ● Top quality prints by new process
- ● Fast, automated; from 1p per print
- ● Choice of picture size, print or film

Tudorcape Ltd. 28, Southwood Lane, London N6.



ILFORD shows up everywhere.

The performance you expect – and get from ILFORD X-ray materials shows up in many other, sometimes unexpected places.

For if there's an image to be recorded, ILFORD will seldom be far away.

Our Microfilm products show up in the computer world recording output and in the fields of finance and industry with image retrieval systems. And again in the security recording of the massive weekly tide of football pool coupons.

We show up again in newspapers and magazines where ILFORD films and papers provide the illustrations which are often converted into print by ILFORD Graphic Arts materials.

Our Photographic products can show up everywhere from banks (Surveillance film for high security areas) to outer space (Nuclear emulsions as used in every U.S. space shot so far).

In Colour Printing too – amateur or professional – Cibachrome shows up wherever standards really count. You may not see the name, but you will see the results – everywhere.

It is this very involvement in so many fields that supports the broad fundamental research and keeps the ILFORD products you use efficient and up-to-date.

One last thing from ILFORD that always 'shows up': the after sales and technical service.

ILFORD X-RAY

ILFORD Limited, Basildon, Essex.

There's more to ILFORD than meets the eye

CELLUMARKS

quickly add useful information to the routine names of hospital and patient recorded by the UNIVEX light-operated film marker.

The great majority of legends use $\frac{1}{4}''$ lettering but $\frac{1}{2}''$ is available at the same price.

May we quote you for a set of legends to your particular requirements?

CUTHBERT ANDREWS
BUSHEY VILLAGE, WATFORD

1978, *British Journal of Radiology*, *51*, 943–952
VOLUME 51 NUMBER 612 DECEMBER 1978

The British Journal of Radiology

Current thoughts on fast neutron therapy

The Mackenzie Davidson Memorial Lecture delivered at The British Institute of Radiology on November 17, 1977

By W. Duncan

Department of Radiotherapy, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU

(*Received April, 1978*)

We honour this evening the memory of a great pioneer of British radiology, Sir James Mackenzie Davidson, who was renowned for his skill and compassion as a physician and surgeon, his inventiveness as a radiologist and above all as an inspired teacher. I feel particularly privileged to pay tribute to Sir James Mackenzie Davidson as one of the most distinguished medical graduates of my own Alma Mater, the University of Aberdeen, where he graduated M.B.C.M., in 1882.

He began his career as an ophthalmic surgeon. For a period of ten years until 1895 he was ophthalmic surgeon to Aberdeen Royal Infirmary, during which time he established a reputation as a meticulous surgeon and an imaginative teacher. Mackenzie Davidson had a natural bent for physics and spent much of his spare time carrying out experiments in light and optics, and indeed he enjoyed giving lectures to the public which were lavishly illustrated with impressive experiments. It is perhaps not surprising that on the publication of Roentgen's paper in 1896 he took himself off to Würzburg to interview Roentgen and find out all he could about this new discovery. The following year he decided to leave Aberdeen for practice in London, where he had the opportunity to develop his interests in radiology as consulting surgeon to the X-ray departments of the Royal London Ophthalmic Hospital, Moorfields, and of Charing Cross Hospital.

His professional life was marked by an infectious keenness and his many publications often marked distinct advances in the field of radiology. It seems that Mackenzie Davidson had a continuing interest and enthusiasm for the new, particularly if he could perfect the innovation for clinical application. Neutron radiation would surely have fascinated him and attracted his attention, for the subject of my address today will I feel have a profound influence on the future of radiotherapy.

Early History of Neutron Therapy and Radiobiological Background

The story begins in 1938 when the first clinical trials of fast neutron therapy were undertaken by Stone and Larkin (1942) using the 122 cm cyclotron devised and constructed by Lawrence and Livingstone (1932). The size and complexity of the equipment were enormous in comparison with the compact cyclotrons that are now manufactured for fast neutron therapy. Treatment then was given using a fixed horizontal beam, collimated quite simply within the primary shield which was composed of tanks of water. Many patients with advanced tumours were successfully treated, although it should be remembered that many of them did have severe late effects, particularly in the skin and sub-cutaneous tissues. The reason for the appearance of these

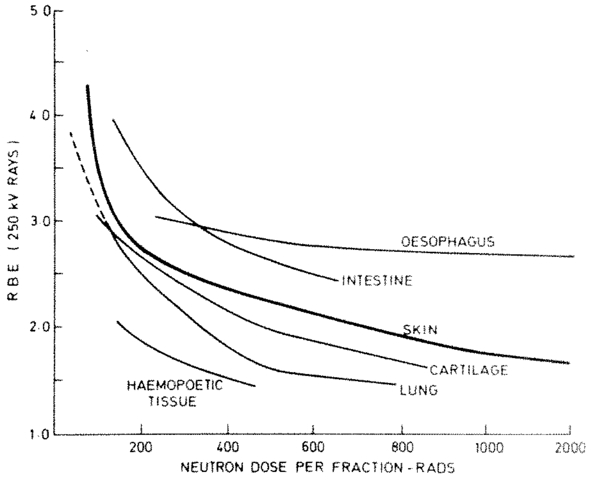


FIG. 1.

The relationship of RBE to dose per fraction of 7 MeV neutrons for different mammalian tissues. (From Field, 1976.)

unexpectedly severe late reactions has been explained by modern cellular radiobiology and described as the "fractionation trap". Field (1976) has shown that the relative biological effectiveness (RBE) of neutrons varies quite markedly with the size of the dose fraction, particularly with dose fractions under about 200 rad, but there is also a large variation in the RBE for different tissues (Fig. 1). Skin and sub-cutaneous tissue has been shown to have RBE values intermediate between those for the alimentary tract and for the haemopoetic system (which has a remarkably low RBE). This changing value of RBE with neutron dose results from the much reduced shoulder on the cell-survival curves following neutron radiation compared to X-irradiation.

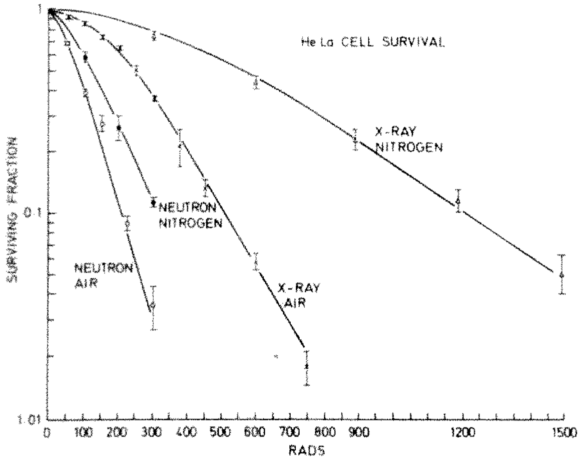


Fig. 2.

Cell survival curves for HeLa cells following irradiation, in air and in nitrogen, with 250 kV X-rays and 14 MeV neutrons. (From Nias *et al.*, 1967.)

Another very important biological difference between the effects of fast neutrons and X rays, the reduced oxygen enhancement ratio, is illustrated in Fig. 2. It was primarily for this reason, the reduction of the "oxygen effect", that it was suggested that there should be a re-evaluation of the therapeutic use of fast neutron radiation.

It is now clear that there are other important differences between the biological effects of neutrons and X rays that may be of clinical significance. Hall and Kraljevic (1976) has shown that there is no recovery from potentially lethal radiation damage after neutron irradiation compared to that normally exhibited following X irradiation. The recovery of chronically hypoxic cells within tumours from potentially lethal damage may well make some tumours relatively resistant to high doses of X rays, but no such protection is afforded following neutron irradiation. Last year Field *et al.* (1976) introduced the concept of what they have called "slow repair" which they have shown to occur in tissues with a low turnover rate such as the lung (Fig. 3), following small dose fractions of X rays. It will be seen that this type of recovery may be demonstrated over a period of at least six weeks whereas after fast neutron irradiation recovery of this type is not seen at all. This means that the phenomenon seen after X irradiation cannot be due to repopulation, which would be similar following neutron irradiation, but must be the result of some intra-cellular repair process that occurs characteristically in slowly regenerating tissues. The effect will also occur in tumour tissues, and so one would expect to see fewer late recurrences than after X irradiation, and this may well be a significant biological factor in contributing to the greater clinical effectiveness of fast neutrons.

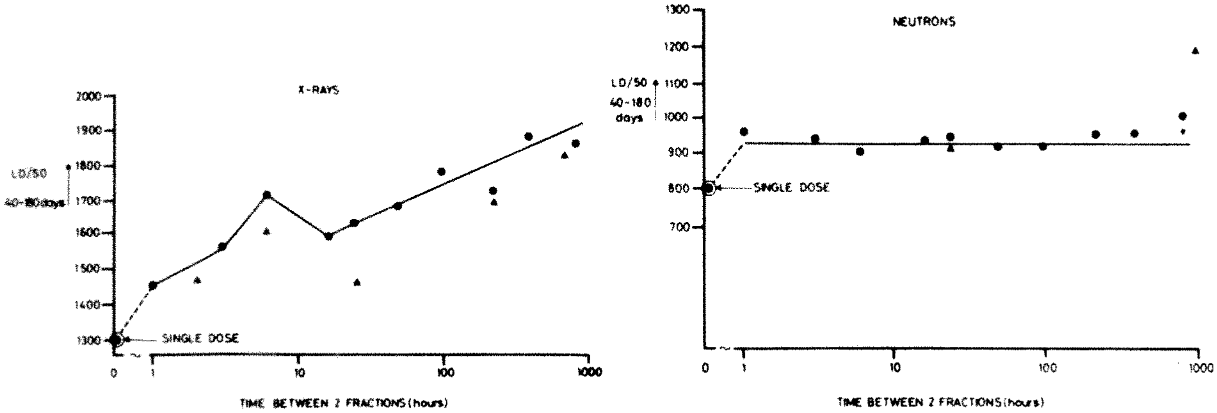


Fig. 3.

The LD50 for lung damage in the mouse after irradiation with two doses of X rays or neutrons. (From Field, *et al.*, 1976.)

A most important consideration in designing clinical trials using fast neutrons concerns the fractionation schedule that should be advised. Important studies have been carried out by Withers *et al.* (1977) by examining the skin reactions in pigs following two, four or five fractions weekly of neutrons or tele-cobalt γ radiation. They have shown that with two fractions of γ rays there is a marked disassociation of relative skin reaction scores between the early and the late responses. With five fractions of tele-cobalt radiation there is no such disparity (see Fig. 4). After fast neutron irradiation there is really no disassociation between early and late effects with fractionation, but it will be seen that the two fraction curves are not quite so closely related as the curves for four fractions. It seems that when using fast neutrons fractionation is less important as far as the relationship between early and late skin reactions is concerned than it is with fractionation using X rays. A similar effect has been demonstrated in the mouse intestine where at doses under 400 rad per fraction of fast neutrons the RBE for immediate reactions is significantly less than that for severe late changes (Geraci *et al.*, 1977).

Another essential radiobiological consideration related to fraction size in clinical radiotherapy is the possibility that with smaller neutron dose fractions the oxygen enhancement ratio may be substantially increased compared to that obtained with large single doses. Hornsey *et al.* (1977) have shown however using the mouse tail model, that with reducing dose per fraction the OER in fact remains low and if anything falls slightly. It would appear therefore that there may be no disadvantage with respect to the OER in giving small daily dose fractions, and there may be some slight advantage with daily fractionation in that closer correlation may be obtained between early reactions and late effects in normal tissues.

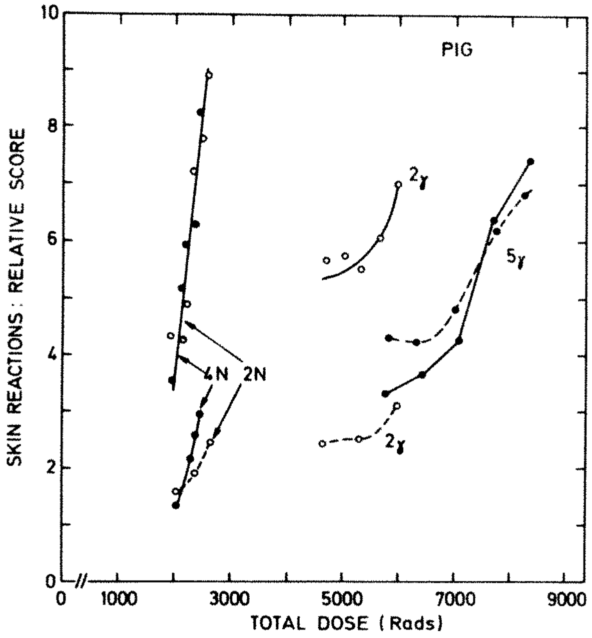


FIG. 4.

The relative score of early and late reactions observed in pig skin. Early reactions are shown as hatched lines. (From Withers *et al.*, 1977.)

A final word about the radiobiological background. Hall and his colleagues (1975) have shown that there is really no great difference in the oxygen enhancement ratio with neutron energy from 2 to 50 MeV, and so obviously higher energy neutron beams are advantageous by virtue of their better penetration without any important loss of their effectiveness in dealing with hypoxic tumours.

NEUTRON GENERATORS

Fast neutron beam generators for clinical use may be based on either a cyclotron or a deuterium-tritium type generator. The choice of cyclotrons may be a multi-purpose large cyclotron or a dedicated compact machine. Large cyclotrons would provide high energy neutron beams but are very expensive and would provide a fixed horizontal or vertical beam. Dedicated mini-cyclotrons have the great advantage of being relatively inexpensive and small enough to be readily situated within or adjacent to Departments of Radiotherapy. The Cyclotron Corporation at present is offering three compact cyclotron facilities, the CS-30 as we have in Edinburgh, and two proton accelerators which are at present under construction, the CP-30 and CP-42. These fixed energy cyclotrons accelerate protons at 30 MeV or 42 MeV on to a thick beryllium target producing neutrons with a 50% depth dose at 12 cm and 14 cm, and dose rates in air at 125 cm of 21 and 47 rad per minute respectively.

The D-T generators have the great attraction for clinical use that they are even more compact machines providing mono-energetic neutrons at 14 MeV. Unfortunately difficulties have arisen in achieving reliable operation at high output with the sealed tube generators such as the Hiletron of Elliott Automation Ltd. Development work is continuing to improve their performance. Another type of sealed tube D-T generator has been made by Philips and has been in regular clinical use since April 1976 in the National Cancer Institute at Amsterdam. Considerable interest is certainly maintained in D-T generators either containing a sealed

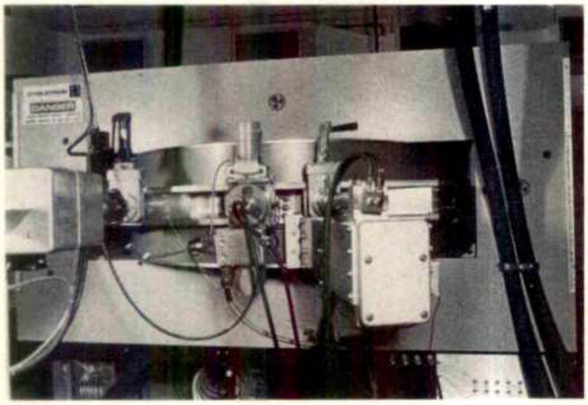


FIG. 5.
The Cyclotron Corporation's CS-30 cyclotron.

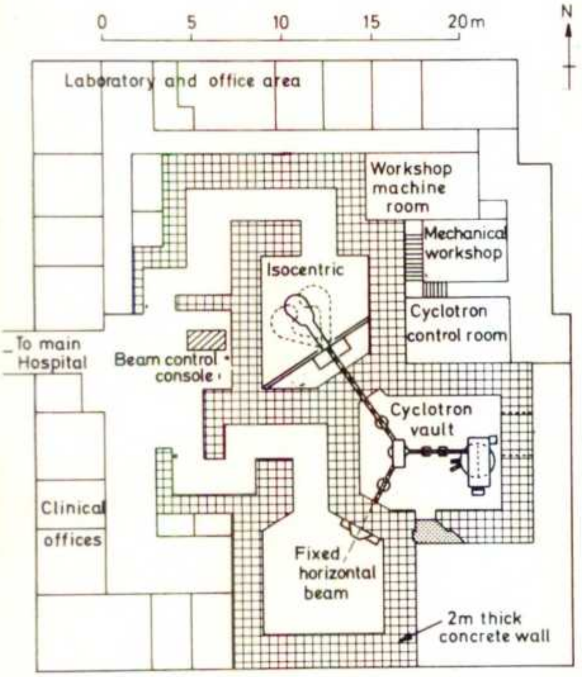


FIG. 6.
Plan of the Edinburgh cyclotron unit.

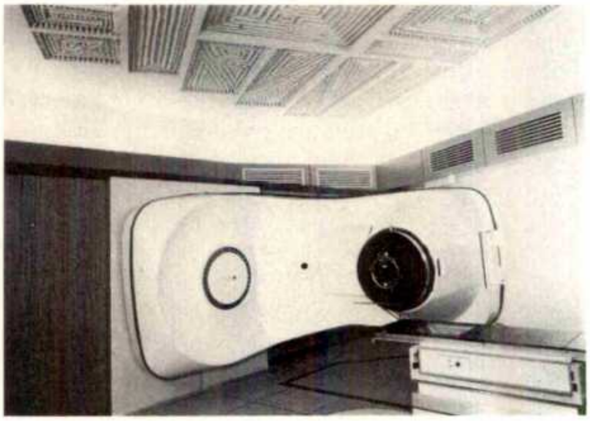


FIG. 7.
The Cyclotron Corporation's iso-centric head for neutron therapy.

tube (for example the Haefely design) or continuously evacuated and which may eventually provide reliable penetrating neutron beams for routine clinical use.

The unit at Edinburgh

Figure 5 shows The Cyclotron Corporation's CS-30 cyclotron installed in Edinburgh. A deuteron beam is extracted from the cyclotron and passes to a beryllium target situated either in the wall of a treatment room or in the shielded head of an iso-centrically mounted machine provided with an interchangeable system of beam collimators, optical field definition and range finding. The lay-out of the Edinburgh cyclotron unit is shown in Fig. 6. It was established by the Medical Research Council with the help of the Lothian Health Board and the Cancer Research Campaign. The unit occupies about 1,500 square metres and is built around the central cyclotron vault and two related treatment rooms, one of which contains the iso-centric therapy machine (Fig. 7) while in the other there is a fixed horizontal beam for radiotherapy based on the Hammersmith design. Both treatment rooms are entered by a labyrinth system to obviate the need for doors. Around the central protected area are situated the control room just to the north of the cyclotron vault and there are workshops, offices and laboratories for physics and engineering staff. There is also a small animal experimental room. The radiotherapy control area joins the link corridor to the X-ray therapy department, and related to the treatment area is a room for secretaries, a clinical suite and a waiting area for patients.

The cyclotron was delivered in April 1976 and commissioning was completed and the first patient treated on March 14, 1977. The operation of the cyclotron has been excellent and we are extremely grateful to Mr. D. D. Vonberg, Director of the Unit, and Mr. T. E. Saxton, the unit manager in Edinburgh, and his team, for the reliable performance of the machine which has been equal to that of our linear accelerators. It was planned to begin clinical studies using the fixed horizontal beam, based on an improved design of that used for some years at the

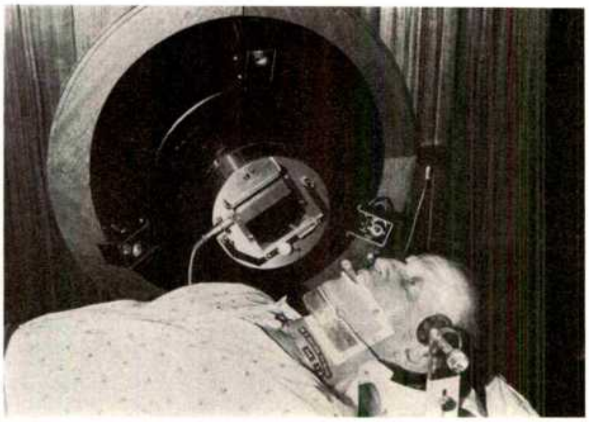


FIG. 8.
The fixed horizontal neutron beam facility.

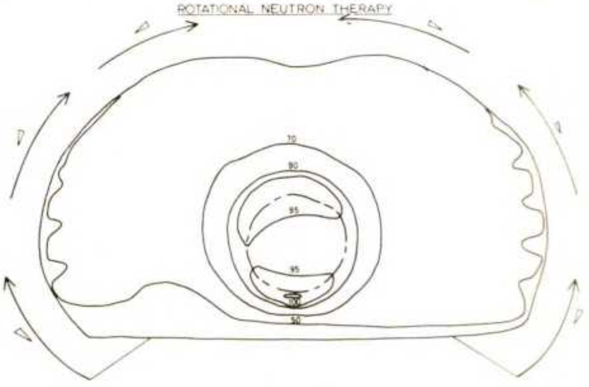


FIG. 9.
A treatment plan for rotational therapy of a bladder cancer using the 7 MeV neutron beam.

MRC Cyclotron Unit at the Hammersmith Hospital (Williams *et al.*, 1978). It will be seen that the facility includes optical range finders using an FSD of 125 cm, optical field and central axis definition, back pointers and fully interlocked wedge filters (Fig. 8). We prefer to treat patients in a lying position whenever possible, but alternatively patients may be treated sitting in a specially designed chair, which also affords support and fixation for the head.

The field definition using compressed wood applicators is excellent, and the wedge angle is satisfactorily maintained at depth (Williams *et al.*, 1978). The 50% depth is 8.9 cm for a 10 × 10 cm field at an FSD of 125 cm and at the present time, using 70% of the maximum beam current, the incident dose rate is about 30 rad per minute.

Treatment planning obviously has to be more complex with 7 MeV neutrons than with megavoltage X rays because of the relatively poor beam penetration, but for the average-sized patient the dose distribution is comparable with that from 4 MV X rays when a parallel opposed pair of fields is employed in the "head and neck" region. In treating a site such as maxillary antrum or a large tumour of the buccal cavity where a "wedged pair" would suffice to give a good dose distribution with 4 MV photons, it is often necessary using 7 MeV neutrons to introduce a third contra-lateral field to achieve a comparable dose distribution within the high dose volume. In treating supra-tentorial tumours the whole brain is irradiated using a parallel-opposed pair of fields on a 4 MV linear accelerator. With fast neutrons a third vertical field needs to be added but this in fact achieves a better dose distribution than what one has been accustomed to accept with high energy photons.

We have now completed treatment on 70 patients (November 1977) but it is of course too early to make any assessment of the tumour responses and normal tissue reactions observed so far. In April 1978 the iso-centric neutron therapy machine will be brought into clinical use and in due course will be capable of rotational therapy. The dose distribution chart shown in Fig. 9 shows what can be achieved in treating a bladder cancer by a rotational technique with neutrons of a mean energy of about 7 MeV.

RESULTS OF NEUTRON THERAPY

The continuing interest and indeed enthusiasm for fast neutron therapy is undoubtedly due to the remarkable clinical results that have been reported from the MRC Cyclotron Unit at the Hammersmith Hospital. In 1975 Catterall *et al.*, reported the results of the first randomly controlled trial of patients with advanced cancers of the head and neck region. These tumours, of many different sites, tumour types and stages of advancement, were randomized after a unique system of stratification for treatment by megavoltage X rays or the 7 MeV neutron beam. Using 7 MeV neutrons, a standard treatment giving a dose of 1560 rad in 12 fractions over four weeks was required by most patients, but there were large differences in the dose and fractionation schedules used in the group of patients treated with photons. They demonstrated a statistically significant improvement in local control of these tumours following neutron therapy, 37 out of 52 patients having complete tumour regression compared to only seven out of 50 patients treated with photons. The distribution of relative doses has shown that the patients treated with neutrons had a higher average tumour dose and less spread of dose than those treated by

TABLE I

Results of randomly controlled trial advanced head and neck cancers

Radiotherapy	Patients	Complete regression	Later recurrence	Local tumour control
Neutrons	70	54	1	53 (75.7%)
Photons	63	27	15	12 (19.0%)

From MRC Cyclotron Unit, Hammersmith Hospital (Catterall, *et al.*, 1977).

TABLE II

Results of randomly controlled trial advanced head and neck cancers

Morbidity	Photons	Neutrons
	Mean TDF = 113	Mean TDF = 119
Patients at risk	45	58
Eye	1	2
Spinal cord	0	1
Laryngo-pharynx	1	9
Total complications	2 (4%)	12 (21%)

From MRC Cyclotron Unit, Hammersmith Hospital, (Catterall *et al.*, 1977.)

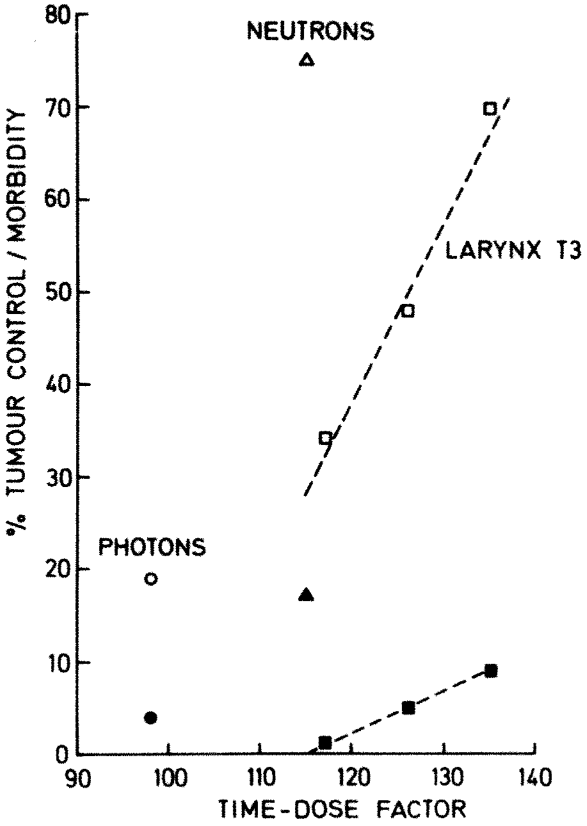


Fig. 10.

The results of the Hammersmith "head and neck" trial, local tumour control (△ neutrons O photons) and morbidity rates (▲ neutrons ● photons) compared with the results for T3 larynx cancer of Stewart and Jackson (1975) (☐ tumour control ■ morbidity).

photons. In addition a value of three was used for the RBE of the neutron radiation in the calculation of the dose-time factors, and if this indeed is an under-estimate, as it may well be, the difference in average tumour doses for photons and neutrons would be even greater. The possibility has to be considered that the difference in local tumour control rates could be largely explained by the higher doses given to the patients treated by fast neutrons. It must be acknowledged that Dr. Catterall and her colleagues do not accept this argument and claim that more detailed analysis of their results confirm that patients treated with fast neutrons do show significantly better tumour control at equivalent dose levels. However if one examines one small group of patients with tumours of the oral cavity and oropharynx treated in this trial, the local control rate following neutron therapy is 73% compared with 33.3% following photon therapy. In a pilot study of neutron therapy in the United States reported by Hussey *et al.* (1976), 103 patients with similar tumours were treated and local cancer control was achieved in only 42%, not greatly different from the results achieved by photon therapy in the Hammersmith trial, although their treatment schedule was different.

Catterall *et al.* (1977) have recently published a further report of the randomly controlled trial which corroborates their earlier published results, showing a local tumour control of 75.7% in the neutron treated group compared to 19% in those treated by photons (Table I). This last report gives some details about the morbidity of patients treated by neutrons and photons as shown in Table II. It will be seen that there is a considerably higher number of serious complications in the group of patients treated by neutrons, and this may again be an indication that the physical dose of radiation delivered in this group of patients was higher than that given to the photon group. The problem of comparability of these results is illustrated in Fig. 10. The results of the MRC trial report (Catterall *et al.*, 1975) are illustrated and by comparison the results reported by

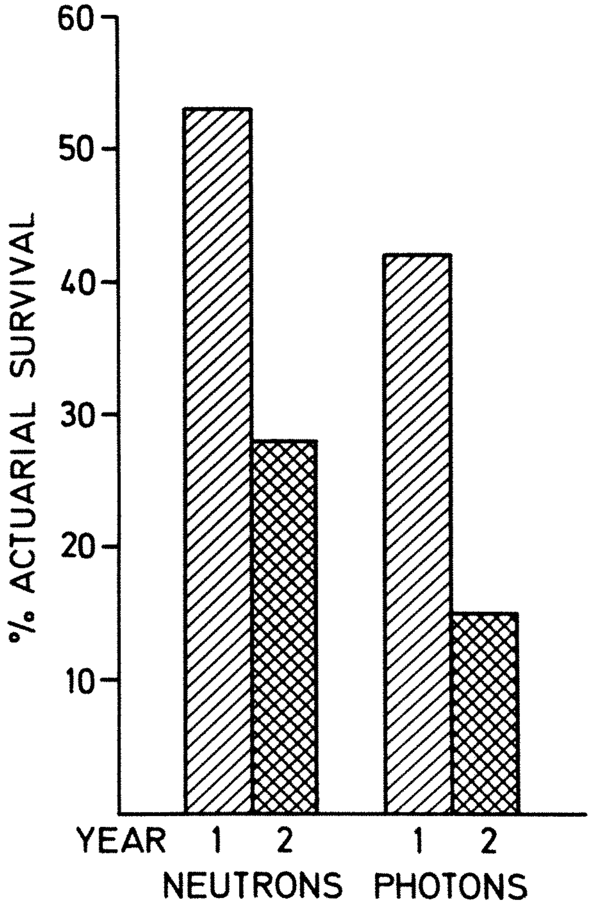


FIG. 11.
Actuarial survival rates of patients in Hammersmith "head and neck" cancer trial. (Catterall *et al.*, 1977.)

TABLE III
ADVANCED HEAD AND NECK CANCERS

Radiation	Patients	Local control	Complications
Neutrons only 2 fractions/week	49	23 (46.9%)	10 (20.4%)
Neutrons only 4 fractions/week	19	7 (36.8%)	1 (5.3%)
Neutron boost	29	14 (48.3%)	5 (17.3%)
Mixed beam	19	11 (57.9%)	0 (0)
"Controls"	49	28 (57.1%)	12 (24.5%)

From MD Anderson Hospital and Tumor Institute, (Peters *et al.*, 1978).

Stewart and Jackson (1975) on the treatment of laryngeal tumours (T3) with photons and the related morbidity are indicated. The steepness of the tumour regression line suggests that the local tumour control rates of patients treated by photons in the Hammersmith trial could well have approached that for neutrons if the physical dose had been increased. Of course one would also expect the morbidity following photons to have increased to some extent. It is important to note the lower morbidity reported by Stewart and Jackson with photons for a TDF of 119, compared to Dr. Caterall's neutron treated series. It should be pointed out that some of this morbidity may be "tumour-related" and the series of Stewart and Jackson included a quite different category of patients, with tumours of a less advanced stage than those managed by Dr. Catterall and her colleagues. It remains essential to determine the relative positions and slope of the dose-response curves for both tumour and normal tissues following photon and neutron irradiation before definite judgment may be made about the possible superiority of neutron therapy.

One would expect, in the case of head and neck cancers which have a low probability of haematogenous spread, to see an improvement in the survival rate which parallels the improved local control rates reported. Figure 11 shows that indeed the survival at one and two years is better in patients treated by neutrons, although this has not yet reached levels of statistical significance.

It was disappointing that the early studies carried out in America (Hussey *et al.*, 1976) do not show similar differences in response rates of patients with head and neck cancer following neutron therapy alone. The Americans then examined the use of fractionation schemes containing photons and neutrons (Caderao *et al.*, 1976). One technique employed a one week "boost" of neutron therapy at the end of a five or six week course of photon irradiation. The alternative was a "mixed beam" technique which applied three photon fractions and two neutron fractions each week for seven weeks. The results (Table III) were compared with "controls" who were patients who met all the criteria for the neutron studies but were treated by photons at a time when the neutron beam was not available. No improvement in the local tumour control rate has been seen, although it is important to point out that in the mixed beam group of patients there was no morbidity associated with the neutron therapy compared to a 24.5% morbidity in the control cases. It is also important to note the reduced rate of complications in patients treated with four fractions a week of neutrons compared to two fractions of neutrons per week. Dr. Hussey and his colleagues from the M.D. Anderson Hospital and Tumor Institute at Houston (Peters *et al.*, 1978) have also used the technique of neutron "boost" or "mixed beam" therapy for treating patients with advanced gynaecological cancers, principally Stage III cancer of the uterine cervix. In these patients a much improved local tumour control rate was achieved using mixed beam therapy (80%) compared to controls (42.1%) for a similar order of morbidity. A similar order of improvement was seen in a group of patients with locally advanced prostatic cancer in whom 14 out of 16 patients (87.5%) showed local tumour control when treated with neutrons, compared with only four out of seven (57.1%) of photon-treated controls. The response of locally advanced breast cancers was also evaluated following neutron radiation alone, neutron "boost" and a "mixed beam" technique. There was really no great improvement in local tumour control rates after neutron therapy compared with controls (60%). It was observed that in patients with breast cancer treated by two fractions of neutrons per week there was a great increase in morbidity which was unacceptably high (37.5%), although the local control rate (75%) was the same as that following "mixed beam" therapy which was associated with no morbidity.

Eichhorn and Lessel (1976) have also used "mixed beam" techniques in treating patients with inoperable lung cancer. Local tumour control has been assessed at autopsy by the absence of tumour histologically within the irradiated volume. These patients were not treated within a randomly controlled trial, but they claim a significant improvement in local tumour control in patients receiving mixed beam therapy (52%) compared to photons alone (32%).

A group of tumours about which there seems to be no controversy on the superiority of neutron therapy is in cancers of the salivary glands. Catterall (1974) has reported from the Hammersmith Hospital a series of 17 patients who had very advanced inoperable tumours, 15 of whom had complete tumour regression—a quite remarkable response rate. One of these patients did suffer a radio-necrosis of the temporal lobe, but there was no other recorded morbidity. Hussey *et al.* (1976) from the United States also reported a series of 14 patients with inoperable salivary gland tumours, of whom 10 had local tumour control and only one patient had significant morbidity.

It is generally agreed that the response of brain tumours to photon radiation is extremely disappointing. It was to be hoped that fast neutrons might hold the possibility of considerable improvement, since it is believed that many cerebral tumours contain a proportion of hypoxic cells. Parker and his colleagues (1976) from Seattle in the U.S.A. had earlier reported no improvement in the survival of patients treated by neutrons, and described a rapidly fatal syndrome presenting with evidence of cerebral degeneration some months following neutron therapy. A randomly controlled trial has been started at the MRC Cyclotron Unit by Catterall in association with Bloom of the Royal Marsden Hospital and the Atkinson Morley Hospital (Bloom and Caterall, 1977). All patients had stage III or IV astrocytomas and had undergone substantial surgical removal of the tumour. Initially the dose of 1560 rad was given in four weeks. The syndrome of increasing dementia and subsequent death was again recognized and the radiation dose was reduced. They then prescribed a neutron dose of 1300 rad which was subsequently increased to 1440 rad in four weeks because of evidence of persistent tumour at the lower dose, but unfortunately there was no difference in survival rates. In the photon-treated series there was no clinical evidence of radiation morbidity in the brain. The autopsy data however provide further information of great interest and value. In this series of patients seven of the 33 patients treated by photons had autopsies and all had evidence of residual tumour. Eleven of the 30 patients treated by neutrons had autopsies and five had evidence of tumour of whom two had only microscopic evidence of residual tumour. In the series of patients reported by Parker *et al.* (1976) from Seattle, 15 of 36 who underwent neutron irradiation were autopsied, and of these ten were found to be free of tumour. Only one showed evidence of residual tumour, and in the 14 others there was only necrotic collagenous debris at the site of the tumour. There were however widespread changes of demyelinization. It seems therefore that the level of dosage in treating cerebral tumour is critical, and there is a high probability of producing serious high dose effects in the central nervous system if the tolerance dose is exceeded.

CONCLUSION

Most of the patients treated by fast neutrons in these early clinical trials have had very advanced tumours indeed, and have been included in what should be regarded as preliminary "dose-fractionation" studies. They have shown that tumour responses following neutron irradiation are highly encouraging, particularly in epithelial cancers of the head and neck region and also in other tumours that are listed in Table IV. In the case of localized breast

TABLE IV

TUMOUR RESPONSES TO FAST NEUTRONS

Advantages
Head and Neck Cancer Squamous Cell Ca and Others Gynaecological Cancer Bronchial Cancer Parotid Tumours Soft Tissue Sarcomas Gastric Cancer Colo-rectal Cancer
Doubtful advantage
Breast Cancer Brain Tumours

TABLE V

NORMAL TISSUE RESPONSES TO FAST NEUTRONS

Advantages	
Lung	Improved Tolerance
Bone marrow	High Tolerance
Abdomen	Reduced Radiation Sickness
Bone and cartilege	Reduced Absorption
Disadvantages	
Skin	Lack of Sparing
Subcutaneous tissue	Increased absorption
Central nervous system	No Recovery
Eye	Reduced tolerance

cancer and brain tumours there may be little or no advantage in neutron irradiation, perhaps in both because of the selective increased absorption of neutrons in fatty tissue. When one considers the normal tissue reactions to neutrons it is clear that while there are advantages there are also relative disadvantages to be recognized (Table V). At the present time too it must always be remembered that most neutron beams available for clinical use are limited by poor penetration, lack of manoeuvreability of the beam or both, resulting in certain restrictions on their optimal clinical application. It is however necessary to complete this initial period of clinical evaluation with the facilities presently available until the role of neutron therapy is properly established. Only then would it seem justifiable to support further technological research to improve neutron therapy machines for routine clinical use.

Much pioneering work remains to be undertaken. James Mackenzie Davidson was always insistent on the fundamental value of physics in radiology, and I am sure that he would be equally insistent today on the essential importance of modern technology and radiobiology to radiation therapy. I feel confident that the influence of this Institute will ensure that we continue to attract young members with the enquiring and innovative spirit of James Mackenzie Davidson. It will be by their efforts in physics, engineering and biology as well as in clinical practice that we will overcome the difficulties and elucidate the uncertainties that remain about the production and therapeutic application of fast neutrons. There is no doubt that fast neutron radiation offers promise of considerable improvement in cancer control; continuing clinical evaluation of neutrons will have a far-reaching influence on the future philosophy and practice of radiotherapy.

REFERENCES

BLOOM, H. J., and CATTERALL, MARY, 1977. Paper read at 10th International Congress of Radiology, Rio de Janeiro.

CADERAO, J. B., HUSSEY, D. H., FLETCHER, G. H., SAMPIERE, V. A., JOHNSON, D. E., and WHARTON, J. T., 1976. Fast neutron radiotherapy for locally advanced pelvic cancer. *Cancer*, *37*, 2620–2629.

CATTERALL, MARY, 1974. The treatment of advanced cancer by fast neutrons from the Medical Research Council's Cyclotron at Hammersmith Hospital, London. *European Journal of Cancer*, *10*, 343–347.

CATTERALL, MARY., BEWLEY, D. K., and SUTHERLAND, I., 1977. Second report on results of a randomised clinical trial of fast neutrons compared with X or gamma rays in treatment of advanced tumours of the head and neck. *British Medical Journal*, *1*, 1642.

CATTERALL, MARY, SUTHERLAND, I., and BEWLEY, D. K., 1975. First results of a randomised clinical trial of fast neutrons compared to X or gamma rays in treatment of advanced tumours of the head and neck. *British Medical Journal*, *2*, 653–656.

EICHHORN, H. J., and LESSEL, A., 1976. A comparison between combined neutron and telecobalt therapy with telecobalt therapy alone for cancer of the bronchus. *British Journal of Radiology*, *49*, 880–882.

FIELD, S. B., 1976. An historical survey of radiobiology and radiotherapy with fast neutrons. *Current Topics in Radiation Research Quarterly*, 11, 1–86.

FIELD, S. B., HORNSEY, S., and KUTSUTAWI, Y., 1976. Effects of fractionated irradiation on a mouse lung and a phenomenon of slow repair. *British Journal of Radiology*, *49*, 700–707.

GERACI, J. P., JACKSON, K. L., CHRISTENSEN, G. M., THROWER, P. D., and WEYER, B. J., 1977. Acute and late damage in the mouse small intestine following multiple fractionations of neutrons or X-rays. *International Journal of Radiation Oncology, Biology and Physics*, *2*, 693–696.

HALL, E. J., and KRALJEVIC, URSULA, 1976. Repair of potentially lethal damage: comparison of neutron and X-ray RBE and implications for radiation therapy. *Radiology*, *121*, 731–735.

HALL, E. J., ROIZIN-TOWLE, L., and ATTIX, F. H., 1975. Radiobiological studies with cyclotron-produced neutrons. *International Journal of Radiation Oncology, Biology and Physics*, *1*, 33–40.

HORNSEY, S., ANDREOZZI, U., and MYERS, R., 1977. Factors to be considered in deciding on fraction size for neutron therapy. *Radiobiological Research and Radiotherapy Vol. II*, 49–59. IAEA, Vienna.

HUSSEY, D. H., PARKER, R. G., and RODGERS, C. C., 1976. A preliminary report of the fast neutron therapy pilot studies in the United States. In *Particle Radiation*

Therapy Proceedings of International Workshop, American College of Radiology, *11*, 435–450.

Lawrence, E. O., and Livingstone, M. S., 1932. A magnetic resonance accelerator. *Physiology Review, 40*, 19–23.

Nias, A. H. W., Greene, D., Fox, Margaret, and Thomas, R. L., 1967. Effect of monoenergetic neutrons on HeLa cells and P.388F cells *in vitro*. *International Journal of Radiation Biology, 13*, 449.

Parker, R. G., Berry, H. C., Gerdes, A. J., Soronen, M. D., and Shaw, C. M., 1976. Fast neutron radiotherapy of glioblastoma multiforme. *American Journal of Roentgenology, 127*, 331–335.

Peters, L. J., Hussey, D. H., Fletcher, G. H., Baumann, P. A., and Olson, M. H., 1978. A preliminary report of the MDAH-TAMVEC fast neutron therapy pilot study. *American Journal of Roentgenology*, (in press).

Stewart, J. G. and Jackson, A. W., 1975. The steepness of the dose response curve both for tumor cure and normal tissue injury. *The Laryngoscope, 85*, 1107–1111.

Stone, R. S. and Larkin, J. C., 1942. The treatment of cancer with fast neutrons. *Radiology, 39*, 608–614.

Williams, J. R., Law, J., Bonnett, D. E. and Parnell, C. J., 1978. Initial experiences with the fast neutron facility at Edinburgh. In *Proceedings of the Third Symposium on Neutron Dosimetry in Biology and Medicine, Neuherberg/München*, 1977.

Withers, H. R., Flow, B. L., Huchton, J. I., Hussey, D. H., Jardine, J. H., Mason, K. A., and Smathers, J. B., 1976. Effect of dose fractionation on early and late skin responses to gamma rays and neutrons. *Cancer, 37*, 39–47.

Book review

Biological Effects of ^{224}Ra. Benefit and Risk of Therapeutic Application. Edited by W. A. Müller and H. G. Ebert. 1978 pp. 235, illus., (Martinus Nijhoff, The Hague) Hfl.62.50.

The book recounts the proceedings of a symposium at Neuherberg/Munich in September 1976 held to provide a forum where clinicians and experimentalists using ^{224}Ra and similar radionuclides could present and mutually assess their work.

Of the five sessions into which the symposium was divided three dealt mainly with the clinical findings in ankylosing spondylitis and its treatment with ^{224}Ra and included also evaluations of the use of the radionuclide in the treatment of rheumatoid arthritis and Paget's disease. A paper dealing with X-ray therapy of ankylosing spondylitis was also included in this section.

The fourth session consisted mainly of accounts of early and late effects induced experimentally in animals by ^{224}Ra and other α-emitters but also included results updating the documentation of the (probably unjustified) use of ^{224}Ra in the treatment of tuberculosis which began in Germany about 1950.

The papers presented in session five evaluated the risks to man from ^{224}Ra, calculated from experimental and epidemiological findings and predicted by applying a mathematical model of the carcinogenic action of α-emitters.

There are few transcription errors and the tables and diagrams, although diverse in style, are generally clear. However, the reproduction of photographs, particularly those of histology, is often poor. The reports of the two round table discussions held at the end of the symposium only partly compensate for the absence of individual discussions with each paper but may help the reader to judge whether the symposium was successful in its stated aim. Certainly the arguments surrounding dose threshold and the relative merits of ^{224}Ra and X-ray treatment of ankylosing spondylitis were aired and decisions were made. It is perhaps inevitable that discussion about the effects on man should be dominant, but an experimentalist might be forgiven for wishing that space had been specially allotted for discussions of the intriguing results presented of animal experiments carried out notably in Neuherberg and Prague.

However, for any reader already partly informed on this subject the book offers much information which is the more useful in that both experimental and clinical findings are given.

In short, the book is timely and worth its space on the shelves of those clinicians and experimentalists working with ^{224}Ra and similar radiodnuclides or with radiation therapy procedures.

E. R. Humphreys.

1978, *British Journal of Radiology*, *51*, 953–955

Obstructive jaundice and portal vein calcification

By R. L. Mackenzie, B.Sc., M.D., H. R. Tubbs, M.B., M.R.C.P., J. W. Laws, M.B., F.R.C.P., F.R.C.R., J. L. Dawson, M.S., F.R.C.S., and R. Williams, M.D., F.R.C.P.

Liver Unit and Departments of Radiology and Surgery, King's College Hospital and Medical School, Denmark Hill, London, S.E.5.

(*Received May, 1977*)

ABSTRACT

Two patients with extrahepatic portal vein obstruction are described in whom calcification within the thrombus was identified during investigation for obstructive jaundice. Evidence from percutaneous cholangiography in one, and endoscopic cannulation of the common bile duct in the other, supported the view that the common bile duct was being partially compressed by the calcified cavernoma.

In cavernomatous transformation of the portal vein, calcification commonly occurs within the thrombus. However, it is usually slight and found only when the pathological specimen is examined, although it may occasionally be picked up on radiological examination during life (Haddow and Kemp-Harper, 1967; Blendis *et al.*, 1968; Losowsky and Walker, 1968). This paper is concerned with two patients in whom calcification within the portal venous system was identified during investigation for obstructive jaundice, and in whom it appeared that the common bile duct was partially compressed by the calcified cavernoma.

CASE REPORTS

Case 1

This 42-year-old housewife was noted to have splenomegaly at the age of 12, presumably the consequence of an extrahepatic portal vein thrombosis, although this diagnosis was not made until 29 years later. Over the years her medical history was unremarkable except for two episodes of cholestatic jaundice, when 25 and 27 years old, occurring some two weeks post-partum and lasting for about a month.

At the age of 41 she presented with an eight-week history of pruritus, persistent right-sided hypochondrial pain, progressive jaundice and pale stools. Serum bilirubin rose from 9 mg/100 ml on admission to 20 mg/100 ml over the subsequent 35 days. The highest serum alkaline phosphatase level recorded was 32 KA units and both SGOT and prothrombin times were normal. Radiological examination revealed a worm-like band of calcification running transversely across the abdomen at the level of L_1. Subsequently a percutaneous transhepatic cholangiogram (Fig. 1) was carried out which showed an extrinsic narrowing of the common hepatic duct with dilated intrahepatic duct radicals, the band of calcification intersecting the plane of the common hepatic duct at the area of narrowing. Below the narrowing, the common bile duct was normal. A technetium liver scan (Fig. 2) showed a filling defect in the porta hepatis and ultrasound confirmed this, suggesting in addition that the defect was formed by a group of vessels. Liver biopsy appearances were consistent with large duct obstruction.

At laparotomy it was apparent that the portal vein was completely obliterated, being replaced by multiple collateral vessels in the porta hepatis (splenic vein pressure 267 mm saline). The common bile duct was obscured by the collateral vessels, and the gall-bladder was distended without stones. The second part of the duodenum was opened revealing a chronic peptic ulcer proximal to the papilla but its base did not impinge upon the common bile duct. The papilla was probed with a number 12F bougie. No stones could be demonstrated, and post-operatively the liver function tests returned slowly to normal over a period of weeks.

Case 2

This 56-year-old office manager had been well until the age of 32 when he developed intermittent abdominal pain with jaundice. At operation a small fibrosed gall-bladder was removed, together with a solitary stone in the common duct. There is also a note to the effect that multiple veins surrounded the common bile duct which made the dissection

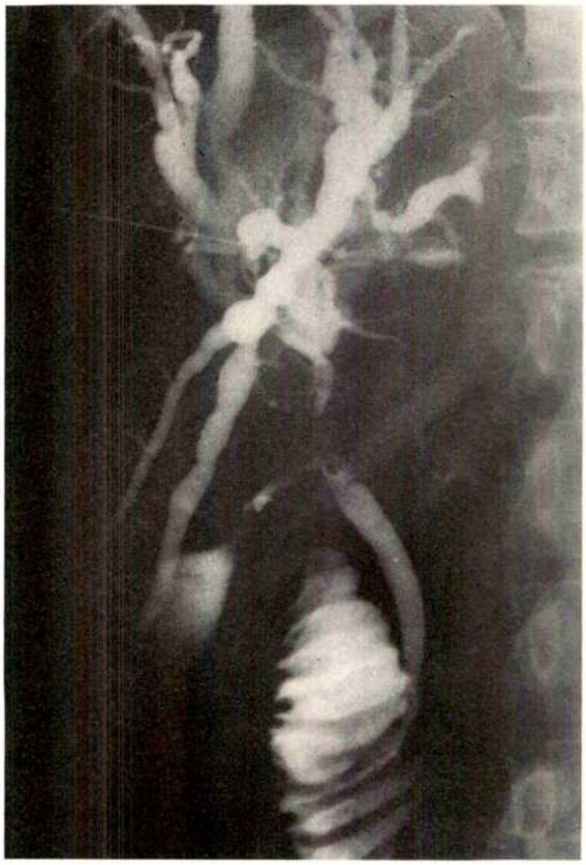


FIG. 1.

Percutaneous transhepatic cholangiogram demonstrating extrinsic compression of common hepatic duct. Note normal gall-bladder and common hepatic duct of normal diameter.

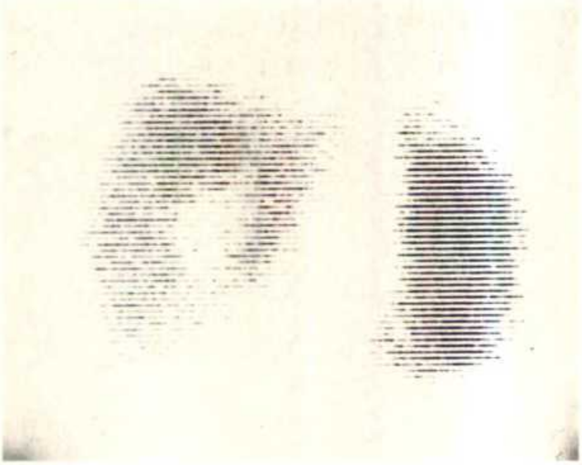


FIG. 2. *Case 1.*
$^{99}\mathrm{Tc}^{m}$ liver scan demonstrating hilar filling defect.

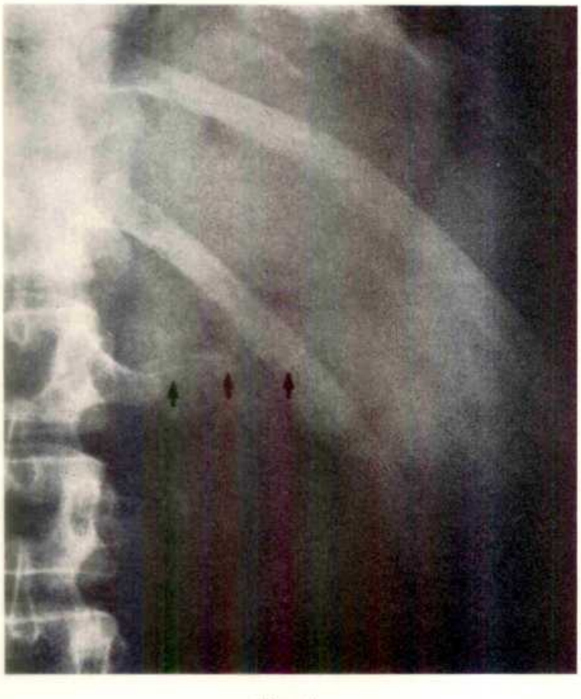


FIG. 3.
Plain roentgenograph of abdomen in Case 2. Note calcification in portal venous system in L.U.Q. corresponding to splenic vein.

difficult. A post-operative T-tube cholangiogram was satisfactory, although there was some narrowing of the preampullary segment. Splenomegaly was first recorded at the age of 37 and one year later he began to have repeated episodes of upper gastrointestinal bleeding from oesophageal varices. The portal vein was found to be thrombosed at laparotomy and ligation of the left gastric vessels and oesophageal veins was performed.

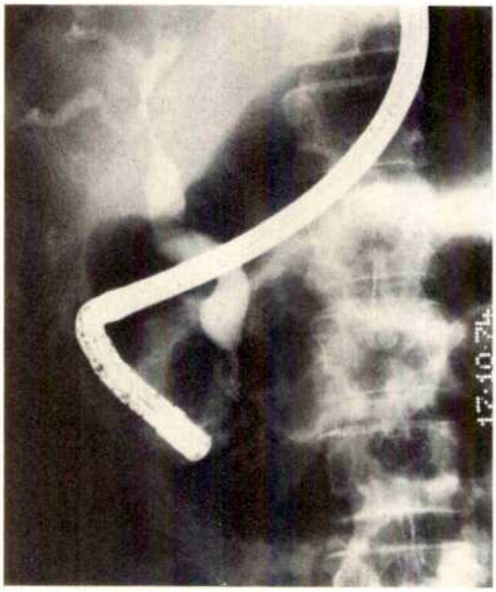


FIG. 4.
ERCP in Case 2 showing generalized dilation of extra- and intrahepatic bile ducts. Note two areas of stenosis, one in pre-ampullary region and one at the level of the CHD.

He was then well for 15 years when bleeding recurred and a trans-thoracic transection of the oesophagus was carried out. Radiological investigations on this occasion revealed calcification within the portal venous system (Fig. 3), an aortoportogram showing extensive dilated collateral vessels in the region of the porta hepatis with complete obstruction of the portal vein. A year later he began to experience episodes of jaundice with fever, due to cholangitis. Endoscopic cannulation of the bile duct (Fig. 4) revealed gross dilatation of the extra- and intrahepatic bile ducts, with compression extrinsically of the common hepatic duct in its upper portion, in addition to the narrowing of the pre-ampullary found previously. This corresponded to the site of a filling defect in the liver scan and the aneurysmal portal vein collaterals on the arterioportogram. No gall stones were seen. Subsequent laparotomy had to be terminated because of profuse haemorrhage from multiple vascular channels, without visualisation of the bile ducts, and finally, after recovery from operation, endoscopic "sphincterotomy" was performed by Dr. P. B. Cotton (Cotton *et al.*, 1976). There was then a gradual return to normal of the serum bilirubin, although the alkaline phosphatase remained elevated.

DISCUSSION

In the sporadic case reports which have appeared (Bleich and Kipen, 1948; Magovern and Muehsam, 1954; Haddow and Kemp-Harper, 1967) since Moberg (1943) first described a case in which the diagnosis of portal vein thrombosis could be made from a plain roentgenograph of the abdomen, the clinical presentation has generally been that of recurrent haemorrhage. In only one case did obstructive jaundice complicate the patient's course and in that case (Sherrick *et al.*, 1964) a stone was found in the common bile duct.

Both of the present cases had deep obstructive jaundice consistent with complete extrahepatic obstruction, but the exact mechanism by which it was produced is not clear. In the first case intraductal stones were eliminated as the cause and the peptic ulcer in the duodenum proximal to the papilla could not be implicated since the common bile duct was not dilated in its lower portion (Fig. 1). The only procedure carried out at surgery was bougie probing of the papilla, and relief of the jaundice may have been a spontaneous one. This may also have happened in the two earlier attacks of obstructive type jaundice which developed in the post-partum period, and which may have been related to a rise in portal pressure for this is known to occur during pregnancy (Gordon and Johnston, 1963). The alternative explanation is that these attacks were due to idiopathic recurrent cholestasis of pregnancy, although this usually occurs in every pregnancy and the last two were uncomplicated by jaundice in this patient. The presence of dilatation above the site where the collateral vessels surround the common hepatic duct, must indicate that these were a major factor in the jaundice. The band of calcification which identifies the location and course of this group of vessels crosses the bile duct at this level and the vascular nature of localized cavernoma in the porta hepatis which was also well shown on the liver scan was confirmed by the ultrasound examination. The hepatocyte can normally secrete bile against a pressure head of 350 mm saline (Watson, 1975), but at the time when the splenic vein pressure was measured (267 mm saline) during the post-operative period the jaundice was already lessening.

Although in the second case there was an earlier history of biliary tract surgery, a number of features suggest that his jaundice was not due to a traumatic stricture. Foremost among these is the normal appearance of the T-tube cholangiogram performed 14 days after his operation. Most traumatic strictures become symptomatic within days of operation and jaundice almost invariably develops within months, whereas this patient did not develop jaundice or cholangitis until 22 years later. The appearances on the endoscopic cholangiogram were also unlike those of a traumatic stricture with tapered superior and inferior margins. Secondly, the calcification visible in the plain roentgenograph of the abdomen, the liver scan, and the aortoportogram localizes the "cavernoma" to a site coincident with the extrinsic compression of the bile duct. The dilatation of the bile duct below this point may have been the consequence of the first episode of obstructive jaundice, for the common bile duct, once dilated, often does not return completely to normal. However, the obstruction due to the "cavernoma" may have been additive to that of the narrowed segment of the pre-ampullary common bile duct for jaundice only remitted completely after the endoscopic "sphincterotomy".

The cause of the portal vein thrombosis in these patients is unknown. None of the known antecedents such as umbilical sepsis or blood dyscrasias were present in either case and neither had underlying liver disease. Calcification is indicative of long-standing thrombosis and certainly the first patient was known to have had splenomegaly from the age of 12, and in the second, veins obscuring the common bile duct were noted at the time of his first operation at the age of 32.

ACKNOWLEDGMENTS

We are indebted to Dr. P. B. Cotton, Consultant Physician at the Middlesex Hospital for his help with the management of the second patient, and to Linda Rimmer for editorial assistance. R.L.M. was supported by the Roscoe Reid Graham Travelling Fellowship at the University of Toronto.

REFERENCES

BLEICH, A. R., and KIPEN, C. S., 1948. Venous calcification in Banti's syndrome. *Radiology, 50*, 657–660.

BLENDIS, L. M., LAWS, J. W., WILLIAMS, R., and THOMSON, W. B., 1968. Calcified collateral veins and gross dilatation of the azygos vein in cirrhosis. *British Journal of Radiology, 41*, 909–912.

COTTON, P. B., CHAPMAN, M., WHITESIDE, C. G., and LEQUESNE, L. P., 1976. Duodenoscopic papillotomy and gallstone removal. *British Journal of Surgery, 63*, 709–714.

GORDON, A. G., and JOHNSTON, G. W., 1963. Portal hypertension in pregnancy. *Journal of Obstetrics and Gynaecology of the British Commonwealth, 70*, 1056–1059.

HADDOW, R. A., and KEMP-HARPER, R. A., 1967. Calcification in the liver and portal systems. *Clinical Radiology, 18*, 225–236.

LOSOWSKY, M. S., and WALKER, B. E., 1968. Liver biopsy and splenoportography in patients with thrombocytopenia. *Gastroenterology, 54*, 241–245.

MAGOVERN, G. J., and MUEHSAM, G. E., 1954. Calcification of the portal and splenic veins. *American Journal of Radiology, 71*, 84–88.

MOBERG, G., 1943. Calcified thrombus in the portal system diagnosed by roentgen examination. *Acta Radiologie, 24*, 374–383.

SHERRICK, D. W., KINCAID, O. W., and GAMBILL, E. E., 1964. Calcification in the portal systems. *Journal of the American Medical Association, 187*, 861–862.

WATSON, C. G., 1975. Evaluation of the patient with suspected extrahepatic biliary obstruction. In *The Surgical Clinics of North America* (Ed) L. C. Carey, pp. 419–425.

1978, *British Journal of Radiology*, *51*, 956–962

Is pancreatogram interpretation reliable?—a study of observer variation and error

By A. Reuben, B.Sc., M.B., B.S., M.R.C.P.,* A. L. Johnson, Ph.D., M.I.S., and
P. B. Cotton, M.D., F.R.C.P.

Gastrointestinal Unit, The Middlesex Hospital, London, and MRC Statistical Research and Services Unit, University College Hospital Medical School, London

(*Received May, 1978*)

ABSTRACT

Observer variation in the interpretation of endoscopic pancreatograms has been examined by asking four experienced observers to assess 40 sets of well-documented radiographs (from 20 patients with cancer and 20 with pancreatitis), both without ("blind") and with clinical details, each on three occasions. Individual consistency for "blind" diagnoses ranged from 61% to 78%, increasing significantly with clinical information. Overall diagnostic accuracy with clinical information varied from 52% to 83% for cancer, and from 87% to 95% for pancreatitis. However, unanimous and correct opinions were given by the four observers for only 53% of all cases, even when clinical details were provided. Clinical information changed the radiographic diagnosis in 43% of assessments, 83% of these changes leading to improved accuracy. ERCP gives direct information about the major pancreatic and biliary duct systems and often provides an accurate diagnosis. Caution must be exercised in relying upon radiological appearances alone.

Endoscopic retrograde cholangio-pancreatography (ERCP) has been welcomed as a major advance in the investigation of patients with pancreatic and biliary tract problems (Editorial, 1972). Careful technique allows a high rate of success with minimal hazard (Cotton, 1977), but serious complications may arise (Bilbao *et al.*, 1976; Belohlavek *et al.*, 1976). Cholangiograms are familiar and usually easy to interpret, but, unlike others (Kasugai *et al.*, 1974; Katon *et al.*, 1974; Rohrmann *et al.*, 1974), we have experienced difficulty in the interpretation of pancreatograms, particularly in distinguishing pancreatitis from cancer. Radiographic interpretation is largely subjective, and observer variation exists in many contexts (Garland, 1959; Geffen *et al.*, 1968; Yerushalmy, 1969; Reger *et al.*, 1974; Schulman and Simpkins, 1975). The present study was undertaken to assess observer performance in pancreatogram interpretation.

MATERIALS AND METHODS

We selected 40 cases in which endoscopic pancreatography had been performed in the standard manner (Cotton, 1972). These comprised the last 20 cases of proven pancreatic cancer from our department, together with 20 similarly reliably documented cases of chronic pancreatitis. Four observers (three gastroenterologists and one radiologist) with personal experience of approximately 200, 1000, 1000 and 2000 ERCP examinations, reviewed the unmarked packets of radiographs. Each observer reported the radiographs independently, three times in different random orders without any clinical information ("blind"). Three "informed" sessions followed, in which reports were given in the knowledge of clinical details, including history, physical examination, laboratory findings, other radiological or isotopic investigations, and the endoscopic appearances at gastro-duodenoscopy. The observers were not told the type nor the distribution of the diagnoses, they had no previous familiarity with the cases and were only told of their performance at the completion of the whole study. The reporters did not agree their diagnostic criteria beforehand; they used their own experience and knowledge of published data. To have agreed criteria before the study would simply have made it a test of memory, when we wished rather to document the degree of disagreement and agreement within and between expert observers. At each session, the observers completed a questionnaire reporting:

1. whether the pancreatogram was normal or abnormal;
2. the diagnosis: probable or definite cancer, probable or definite pancreatitis, some alternative diagnosis, or undecided;
3. the technical quality of the films;
4. the value of clinical information in forming an opinion.

Reports were analysed for the consistency of opinion and accuracy of diagnosis for the measurement of agreement between the observers, and for the influence of the clinical information on reaching a diagnosis.

The consistency of an individual observer was measured by the percentage of cases for which he gave three identical opinions (irrespective of accuracy) in the "blind" or "informed" sessions. Group

---

Correspondence to Dr. P. B. Cotton, The Middlesex Hospital, London W1N 8AA.

*Present address: Department of Gastroenterology, Central Middlesex Hospital, London.

TABLE I

OBSERVER'S RESULTS AND CONSISTENCY FOR ABNORMALITY RATING

Observer	Percentage of abnormal reports		Consistency, %†			
			Individual		Group	
	Blind mean (range)*	Informed mean (range)*	Blind	Informed	Blind	Informed
1	81 (72.5–92.5)	89 (87.5–95)	78	92	65	81
2	92 (90–92.5)	97.5 (97.5)	97	100		
3	97.5 (95–100)	98 (97.5–100)	95	97		
4	89 (81.5–92.5)	91 (87.5–92.5)	84	87		
Mean and significance of differences‡	90 (81–98)	94 (89–98)	89	94		
	Wilcoxon test: $p= <0.005$		Wilcoxon test: $p= <0.025$		Binomial test: $p=0.035$	

*Over three sessions. †See results: normal or abnormal. ‡One-tailed.

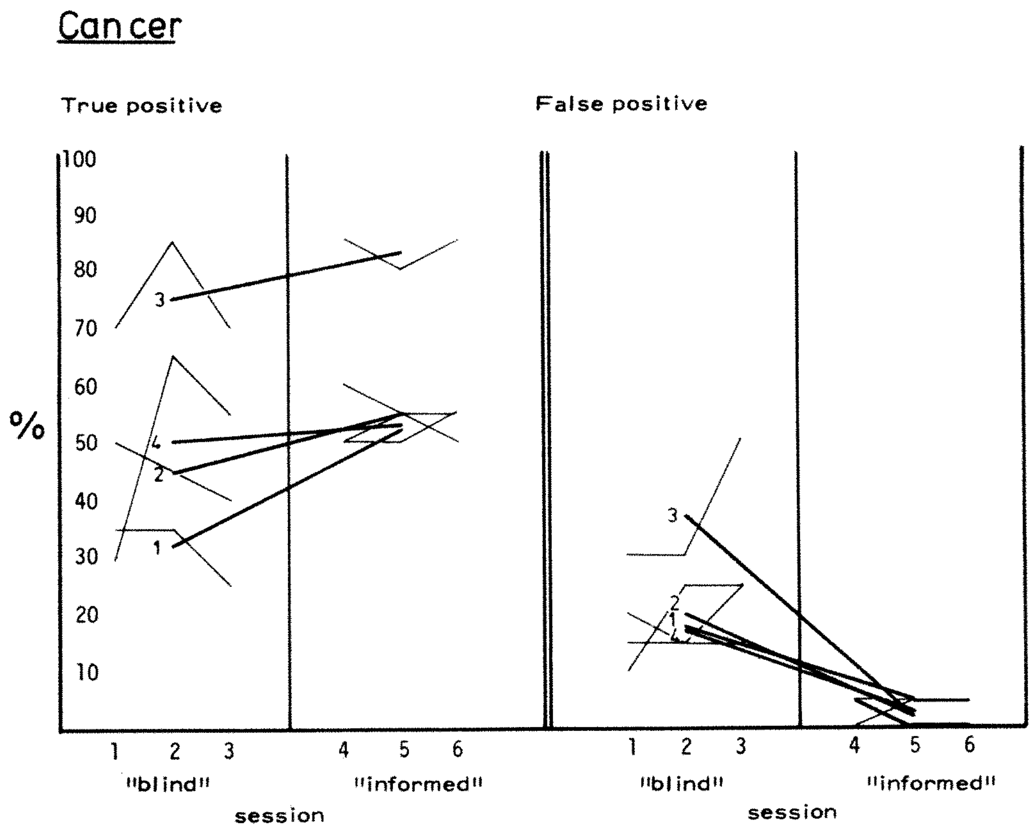


FIG. 1.

Diagnosis of cancer. True-positive and false-positive percentages for the four observers. Bold lines connect mean percentages for the blind and informed sessions for each observer.

agreement (*i.e.* between observers) was measured by the percentage of cases for which 12 identical opinions were given (four observers × three opinions) "blind" or "informed".

Statistical methods

Comparison between the "blind" and "informed" sessions for the percentage of abnormal reports has been made by subtracting the total number of abnormal reports from the four observers over the three "blind" sessions from the total for the three "informed" sessions for each of the 40 sets of films, and applying the Wilcoxon matched-pairs signed-rank test to the resultant differences (Siegal, 1956). Similar comparisons for individual consistency of reporting abnormality, for true- and false-positive percentages and for individual consistency of diagnosis have been made in the same way. "Blind" and "informed" group consistencies for reporting abnormality and for diagnosis have been compared using the binomial test, small-sample adaptation of the McNemar test (Siegal, 1956). One-tailed probabilities have been quoted for all significance tests.

RESULTS

Normal or abnormal (Table I)

All the pancreatograms were from patients with gross pancreatic disease. The observers reported that 90% of radiographs were probably or definitely abnormal for both cancer and pancreatitis, even before clinical information was given (Table I). Three identical reports were given for 78% to 97% of cases examined "blind" and for 87% to 100% with clinical information. Between-observer agreement for abnormality was not so good; 12 identical opinions were given for only 65% of cases seen without clinical information, and for 81% when these details were supplied. The improvement in individual and group consistency with clinical information was statistically significant.

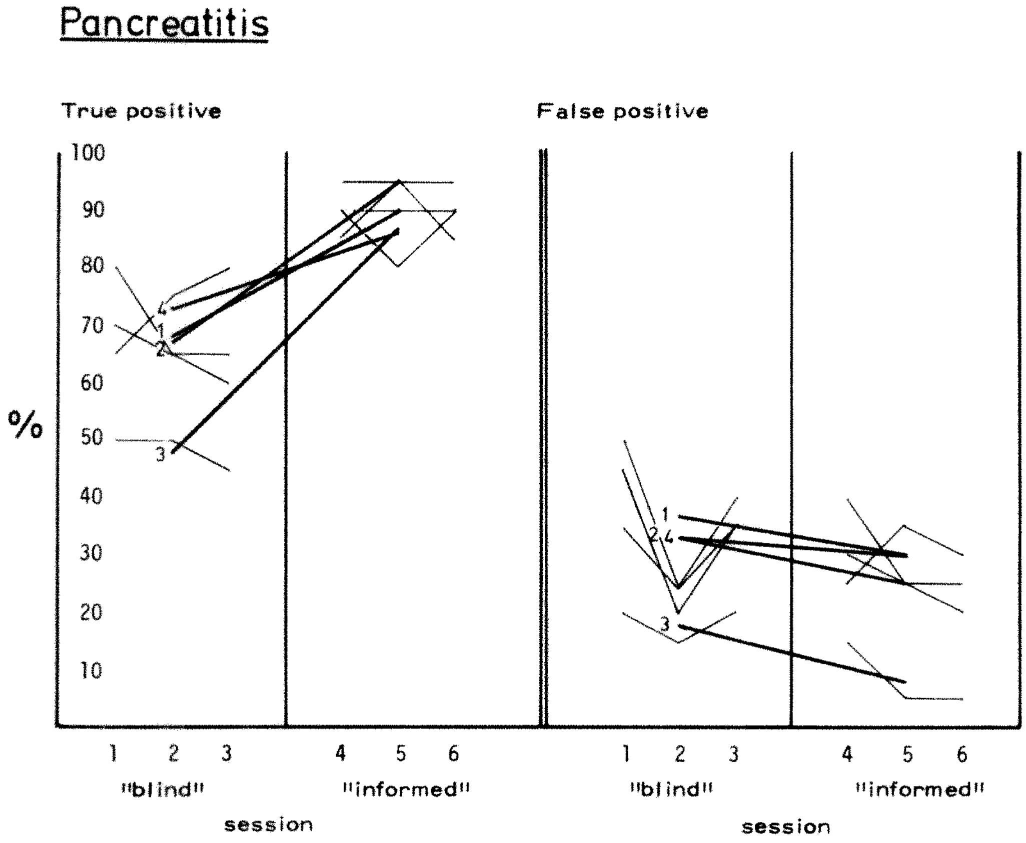


FIG. 2.

Diagnosis of pancreatitis. True-positive and false-positive percentages for the four observers. Bold lines connect mean percentages for blind and informed sessions for each individual observer.

Cancer or pancreatitis

In the subsequent analyses, the probable and definite opinions for cancer and pancreatitis have been amalgamated. Four measures of diagnostic accuracy have been calculated for each observer: true-positive and false-positive percentages for both cancer and pancreatitis (Figs. 1 and 2). The true-positive percentage for cancer is defined as the proportion (× 100) of cancer patients diagnosed as cancer; the false-positive percentage for cancer is defined as the proportion (× 100) of pancreatitis patients diagnosed as cancer.

The proportion of cancer cases correctly identified from the pancreatogram alone was low. The blind true-positive percentages ranged from 32 to 75 (Fig. 1). Many cases of pancreatitis were mistakenly diagnosed as cancer, with average false-positive percentages from 17 to 37. Access to clinical information increased the average true-positive percentages slightly but significantly, from 50 to 61 (Wilcoxon test: $p = <0.025$, one-tailed), and gave a striking and significant reduction in average false-positive diagnoses from 23% to 3% (Wilcoxon test: $p = <0.005$, one-tailed).

The number of pancreatitis cases correctly identified from the pancreatogram alone was slightly higher than for cancer. The blind true-positive percentages for the four observers ranged from 48 to 73 (Fig. 2), with many cancer cases mistakenly diagnosed as pancreatitis (average false-positives 18% to 37%). The percentage of pancreatitis cases correctly identified rose significantly from 64 "blind" to 90 with clinical information (Wilcoxon test: $p = <0.005$, one-tailed). The slight improvement in false-positive diagnosis from 30% to 23% was just significant (Wilcoxon test: $p = <0.05$ one-tailed).

Individual consistency of diagnosis, irrespective of accuracy, varied among the observers from 61% to 78% "blind" and improved to between 75% and 83% with clinical information (Table IIA), the increase being significant. Individual variability is best shown by the changes in percentages that occurred between reporting sessions in each of the four measures (Figs. 1 and 2). Repeated exposure to the radiographs did not result in increasing accuracy. A major sustained improvement occurred only between sessions 3 and 4, after the introduction of clinical information (Figs. 1 and 2). In order to evaluate observer performance realistically, some radiographs were included which were not technically perfect. Results were re-analysed excluding ten sets of films (six cancer, four pancreatitis) which were most frequently poorly rated by all observers; this did not improve the results significantly. Since observers disagreed somewhat concerning their assessment of film quality, further analyses were done excluding each observer's rejects from his own score, again without significant change in result.

Group consistency and accuracy

Individual consistency did not necessarily correlate with between-observer consistency (*e.g.* Fig. 3), and group diagnostic agreement was poor. When probable and definite opinions were combined, 12 identical reports were only obtained for 25% of the cases assessed blindly, and 53% with clinical information (Table IIB).

TABLE II

INDIVIDUAL AND GROUP CONSISTENCY FOR DIAGNOSES

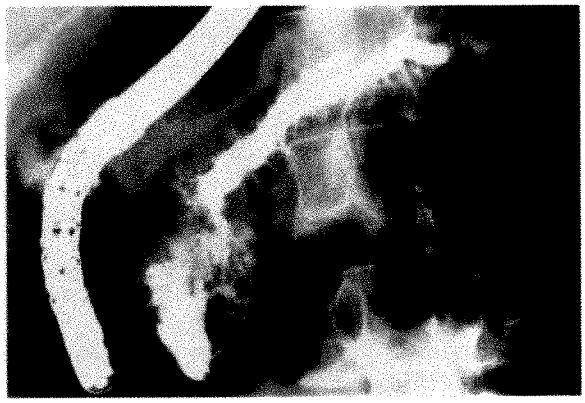
	A		B			
	Individual consistency*, %		Group consistency†, %			
	All diagnoses		All diagnoses		Correct diagnoses	
Observer	Blind	Informed	Blind	Informed	Blind	Informed
1	69	83	25	52	22	53
2	69	83				
3	78	78				
4	61	75				
Mean and significance of differences‡	69	80				
	Wilcoxon test: $p = <0.05$		Binomial test: $p = 0.003$		Binomial test: $p = 0.004$	

*See results: cancer or pancreatitis. †See results: group consistency and accuracy. ‡One-tailed.

The effect of clinical information

The supply of clinical information led to a considerable improvement in diagnostic accuracy (Figs. 1 and 2) and a complete change of opinion in almost half the cases. The change usually led to a correct diagnosis (Table III) or a change from a probable to definite opinion in an already correct diagnosis.

At the first three "blind" sessions, the observers reported the need for clinical information for between 21 and 33 of the 40 cases. When clinical information was supplied in the final three reporting sessions, three of the observers considered it to have been useful in almost every case (36 or 37/40). Observer three claimed to have been influenced by case details in only 20 of the 40 cases; interestingly his results had improved the most in the "informed" reporting sessions (Figs. 1 and 2).



observer	1	2	3	4
opinion	C C C	?C ?C ?C	?C ?C ?C	P P P

FIG. 3.

Blind diagnoses of four observers on a single radiograph, showing individual consistency, but poor between observer agreement.

DISCUSSION

The diagnosis of pancreatic disease sometimes remains difficult despite many new techniques (MacDonald *et al.*, 1976). ERCP has gained widespread acceptance (Cotton, 1977), but two areas of pancreatogram interpretation provide difficulty. The early changes of pancreatitis are difficult to distinguish from variations in the normal pancreas (Cotton, 1974), especially in older patients (Kreel and Sandin, 1973). This study concerned the second problem—the radiographic distinction between cancer and pancreatitis.

Assessment of observer variation is complex and may be defined either by individual deviation from a majority view, or as in this study, by the differences in interpretation among observers examining the same object or between several examinations of the same object by the same observer (Conn and Elkington, 1968). This is independent of the accuracy of interpretation, which is assessed against an independent diagnostic criterion. In our study, the success achieved by the individual observers in identifying the pancreatograms as abnormal (around 90%) was expected since all patients had severe pancreatic disease. Even so, between-observer agreement on this point was comparatively poor. Overall diagnostic accuracy among the individual observers ranged from 52% to 83% for cancer, and from 87% to 95% for pancreatitis with clinical information.

In studies of radiograph interpretation, involving large numbers of observers of similar training, a reciprocal relationship has been noticed between the percentage of true-positive and the percentage of false-positive diagnoses (Lusted, 1971). In spite of similar visual perception, each observer operated with a particular "receiving operating characteristic" (Green and Swets, 1966) influenced by his motivation towards a particular diagnosis, which may reflect previous experience or training (Garland, 1949). In our studies, the supply of clinical information not

TABLE III

EFFECT OF CLINICAL INFORMATION ON OBSERVER OPINION

Observer	Number of cases	No change of opinion			Change of opinion		
		Correct	Incorrect	Total	Correct	Incorrect	Total
1	40	16	8	24	15	1	16
2	40	18	5	23	13	4	17
3	40	17	3	20	17	3	20
4	40	15	9	24	12	4	16
Total	160	66	25	91	57	12	69

only reduced error by reciprocal effects on true-positive and false-positive percentages but improved the consistency of diagnosis and its confidence. The value of clinical information was often only appreciated in retrospect.

Some reports claim that there are abnormalities of the pancreatogram diagnostic of either cancer or pancreatitis (Kasugai *et al.*, 1974; Katon *et al.*, 1974; Rohrmann *et al.*, 1974; Koch *et al.*, 1976; Robbins *et al.*, 1973; Norton *et al.*, 1973; Stadelmann *et al.*, 1974). Whilst greater experience and study may define better criteria, this analysis has reinforced our impression and that of others (Fukomoto *et al.*, 1974; White and Silverstein, 1976) that there is considerable overlap in the radiographic appearances of these two diseases, which may also coexist (Gambill, 1971). Pancreatogram changes are rarely pathognomonic, reflecting the well-recognized overlap of histological changes in these diseases (Elias, 1969).

ERCP is a complex technique with many potential indications in different clinical contexts. It is not entirely without hazard, and we can question whether diagnostic pancreatography can be justified, when unanimous and correct opinions were given by the observers on the radiographs alone for only 22% of the cases. The degree of observer variation was high, but similar to that reported in studies concerning the clinical assessment of hepatomegaly (Blendis *et al.*, 1970), physical signs in the respiratory system (Smyllie *et al.*, 1965), chest radiographs (Reger *et al.*, 1974), isotope liver images (Davies *et al.*, 1972), the classification and histology of Hodgkin's disease (Coppleson *et al.*, 1970) and others (Lusted, 1968).

Our study was a very severe test of pancreatography. The films were not chosen for the quality of the examination, and the observers were not able to collaborate in forming an opinion as happens in the clinical context. Furthermore, the study concerned only one aspect of pancreatography. In many of the patients with pancreatitis, the diagnosis was not clinically in doubt. The procedure was performed in order to provide a logical basis on which to consider surgical intervention—a major role for pancreatography, for which it is well equipped. In the diagnostic context of a patient with obscure pain, an unequivocally abnormal pancreatogram is helpful even if the final distinction between cancer and pancreatitis cannot be made. It is clear that endoscopic pancreatography is not the supreme diagnostic technique in the differentiation of pancreatic diseases. This has led to the development of related techniques such as cytology and biochemistry of pure pancreatic juice collected from within the duct at ERCP (Endo *et al.*, 1974; Hatfield *et al.*, 1976; Cotton and Heap, 1975), and to diagnostic strategies based on several procedures for the identification and diagnosis of pancreatic disorders (DiMagno *et al.*, 1977; Ferrucci and Eaton, 1973; Mitchell *et al.*, 1976). We are currently assessing the respective roles of pancreatography, grey-scale ultrasonography, and computerized tomography in pancreatic imaging (Cotton *et al.*, 1978). Observer variation exists within all these modalities.

ACKNOWLEDGMENTS

We are indebted to Drs. E. Elias, A. Hatfield, M. Kizu and J. Pemberton for taking part in this study, and to Drs. M. Chapman, B. Laurence, T. Heap and H. A. Shapiro for their help in a pilot study.

REFERENCES

BELOHLAVEK, D., KOCH, H., ROSCH, W., SCHAFFNER, O., MAEDER, H. U., FLORY, J., CLASSEN, M., and DEMLING, L., 1976. Five years experience in endoscopic retrograde cholangiopancreaticography (ERCP). *Endoscopy*, *8*, 115–118.

BILBAO, M. K., DOTTER, C. T., LEE, T. G., and KATON, R. M., 1976. Complications of endoscopic retrograde cholangiography (ERCP). *Gastroenterology*, *70*, 314–320.

BLENDIS, L. M., MCNEILLY, W. J., SHEPPARD, L., WILLIAMS, R., and LAWS, J. W., 1970. Observer variation in the clinical and radiological assessment of hepatosplenomegaly. *British Medical Journal*, *1*, 727–730.

CONN, H. O., and ELKINGTON, S. G., 1968. Is hepatic scanning overrated? *Gastroenterology*, *54*, 135–140.

COPPLESON, L. W., FACTOR, R. M., STRUM, S. B., GRAFF, P. W., and RAPPAPORT, H., 1970. Observer disagreement in the classification and histology of Hodgkin's disease. *Journal of the National Cancer Institute*, *45*, 731–740.

COTTON, P. B., 1972. Cannulation of the papilla of vater by endoscopy and retrograde cholangiopancreatography (ERCP). *Gut*, *13*, 1014–1025.

1974. The normal endoscopic pancreatogram. *Endoscopy*, *6*, 65–70.

1977. Progress report ERCP. *Gut*, *18*, 316–341.

COTTON, P. B., DENYER, M. E., KREEL, L., HUSBAND, J., and MEIRE, H. B., 1978. Comparative clinical impact of endoscopic pancreatography, grey-scale ultrasonography and computed tomography (EMI scanning) in pancreatic disease. A preliminary report. *Gut*, *19*, 679–684.

COTTON, P. B., and HEAP, T., 1975. The analysis of pancreatic juice. *British Journal of Hospital Medicine*, *14*, 659–666.

DAVIES, R. J., COTTON, P. B., SWEETLAND, C. A., VERNON, M., and CROFT, D. N., 1972. Comparison of liver scans and liver snaps. *Lancet*, *1*, 927–929.

DIMAGNO, E. P., MALAGELADA, J.-R., TAYLOR, W. F., and GO, V. L. W., 1977. A prospective comparison of current diagnostic tests for pancreatic cancer. *New England Journal of Medicine*, *297*, 737–742.

Editorial. 1972. Cannulation of papilla of vater. *British Medical Journal*, *1*, 459–460.

ELIAS, E. G., 1969. Carcinoma of the pancreas. *Archives of Surgery (Chicago)*, *98*, 138–140.

ENDO, Y., MORII, T., TAMURA, H., and OKUDA, S., 1974. Cytodiagnosis of pancreatic malignant tumours by aspiration under direct vision using a duodenal fibrescope. *Gastroenterology*, *67*, 944–951.

FERRUCCI, J. T., and EATON, S. B., 1973. Radiology of the pancreas. *New England Journal of Medicine*, *288*, 506–510.

FUKOMOTO, K., NAKAJIMA, M., MURAKAMI, K., and KAWAI, K., 1974. Diagnosis of pancreatic cancer by endoscopic pancreatocholangiography. *American Journal of Gastroenterology*, *62*, 210–213.

Gambill, E. E., 1971. Pancreatitis associated with pancreatic carcinoma. A study of 26 cases. *Mayo Clinic Proceedings*, *46*, 174–177.

Garland, L. H., 1949. Scientific evaluation of diagnostic procedures. *Radiology*, *52*, 309–327.

1959. Studies on the accuracy of diagnostic procedures. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *82*, 25–38.

Geffen, N., Darnborough, A., and DeDombal, F. T., 1968. Radiological signs of ulcerative colitis—assessment of their reliability by means of observer variation studies. *Gut*, *9*, 150–156.

Green, D., and Swets, J., 1966. In *Signal detection theory and psychophysics*, pp. 34–35 (John Wiley and Sons, New York).

Hatfield, A. R. W., Smithies, A., Wilkins, R., and Levi, A. J., 1976. Assessment of endoscopic retrograde cholangio-pancreatography (ERCP) and pure pancreatic juice cytology in patients with pancreatic disease. *Gut*, *17*, 14–22.

Kasugai, T., Kuno, N., and Kizu, M., 1974. Manometric endoscopic retrograde pancreato-cholangiography. Technique, significance, evaluation. *American Journal of Digestive Diseases*, *19*, 485–502.

Katon, R. M., Lee, T. G., Parent, J. A., Bilbao, M. K., and Smith, F. W., 1974. Endoscopic retrograde cholangiography. Experience with 100 cases. *American Journal of Digestive Diseases*, *19*, 295–306.

Koch, H., Classen, M., and Demling, L., 1976. *Alterations of the biliary duct system in diseases of the pancreas.* International workshop at Erlangen (Georg Thieme, Stuttgart).

Kreel, L., and Sandin, B., 1973. Changes in pancreatic morphology associated with ageing. *Gut*, *14*, 962–970.

Lusted, L. B., 1968. In *Introduction to Medical Decision Making*, pp. 181–194 (Charles C. Thomas, Springfield, Illinois, U.S.A.).

1971. Decision making studies in patient management. *New England Journal of Medicine*, *284*, 416–424.

MacDonald, J. S., Widerlite, L., and Schein, P. S., 1976. Current diagnosis and management of pancreatic carcinoma. *Journal of the National Cancer Institute*, *56*, 1093–1099.

Mitchell, C. J., Elias, E., Agnew, J. E., Summerfield, J., and Dick, R., 1976. Radional sequence of tests for pancreatic function. *British Medical Journal*, *2*, 1307–1309.

Norton, R. A., Ogoshi, K., Hara, Y., Niwa, M., Paul, R. E. Jr., Tomas, J., and Kawai, K., 1973. Pancreatographic abnormalities due to pancreatic cancer. *Gastrointestinal Endoscopy*, *20*, 13–14.

Reger, R. B., Petersen, M. R., and Morgan, W. K. C., 1974. Variation in the interpretation of radiographic change in pulmonary disease. *Lancet*, *1*, 111–113.

Robbins, A. H., Paul, R. E., Norton, R. A., Schimmel, E. M., Tomas, J. G., and Sugarman, H. J., 1973. Detection of malignant disease by peroral retrograde pancreatico-biliary ductography. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *117*, 432–436.

Rohrmann, C. A., Silvis, S. E., and Vennes, J. A., 1974. Evaluation of the endoscopic pancreatogram. *Radiology*, *113*, 297–304.

Schulman, A., and Simpkins, K. C., 1975. The definition of radiological signs in gastric ulcer and assessment of their validity by interobserver variation study. *Clinical Radiology*, *26*, 311–316.

Siegal, S., 1956. In *Non-parametric Statistics for the Behavioural Sciences* (Town, McGraw-Hill).

Smyllie, H. C., Blendis, L. M., and Armitage, P., 1965. Observer disagreement in physical signs of the respiratory system. *Lancet*, *2*, 412–413.

Stadelman, O., Safrany, L., Loffler, A., Barna, L., Miederer, S. E., Papp, J., Kauffer, C., and Jobbe, A., 1974. Endoscopic retrograde cholangiopancreatography in the diagnosis of pancreatic cancer. *Endoscopy*, *6*, 84–93.

White, T. T., and Silverstein, F. E., 1976. Operative and endoscopic pancreatography in the diagnosis of pancreatic cancer. *Cancer*, *37* (1 suppl.), 449–461.

Yerushalmy, J., 1969. The statistical assessment of the variability in observer perception and description of roentgenographic pulmonary shadows. *Radiology Clinics of North America*, *7*, 381–392.

Book review

Dictionary of Abbreviations in Medicine and the Health Sciences. By Harold K. Hughes, pp. xxi+314, 1977 (Lexington, Mass. and Toronto, Lexington Books), £14·40.

Daily life in medicine without abbreviations would be intolerably tedious and pedantic, but I also spend a small part of the day frustrated by them. This is particularly so when I see an X-ray request form by a specialist who has forgotten that his jargon may not be intelligible outside his small world. Or it may be ambiguous—is RTA road traffic accident or renal tubular acidosis, is MI mitral incompetence or myocardial infarct? This book is an excellent stand-by. Its 300 pages are crammed with explanations for all sorts of abbreviations, British as well as American. It is still FFR, not FRCR, and the entries leading up to this are a sample of the range of the dictionary: FFI (free from infection), FFL (firefly luciferase), FFM (fat-free mass; Fellowship for Freedom in Medicine), FFP (fresh frozen plasma). There are of course interesting surprises—did you know about AAACRR (American Association of Academic Chief Radiology Residents)? Sprinkled through the book are words which are not abbreviations at all, like brownie, doll, ripper—the large collection of slang names for drugs of abuse, in this case amphetamine tablets. Hunters for the absurd will not be disappointed, for instance SCRAP (simple complex reaction-time apparatus). I was saddened not to find COWDUNG, even though it cheats: the late C. H. Waddington's splendid term for the Conventional Wisdom of the Dominant Group. All in all a very good and helpful book, mainly for medical libraries, but also welcome for radiologists.

Thomas Sherwood.

1978, *British Journal of Radiology*, *51*, 963–967

Lateral subluxation of the atlas in rheumatoid arthritis

By R. W. Bunton, M.B., Ch.B., D. M. Grennan, M.D., Ph.D., M.R.C.P., D. G. Palmer, M.D., M.R.C.P., F.R.A.C.P.

Department of Medicine, University of Otago Medical School, Dunedin, New Zealand

and R. T. D. de Silva, D.M.R.D. (Lond), M.R.A.C.R., F.R.C.R.

The Department of Radiology, Dunedin Public Hospital

(*Received March, 1978*)

ABSTRACT

Two patients with lateral subluxation of the atlas resulting from rheumatoid disease involving the upper cervical spine have been described. The deformity can be suspected on clinical grounds and in one of our two patients spinal cord damage was a sequel. Erosion of the opposing surfaces of the odontoid and lateral masses of the atlas with detachment of the transverse ligament and deeper fibres of the posterior longitudinal ligament appear to underlie this deformity. Radiological confirmation may require AP views with the head tilted to one or other side.

Atlanto-axial subluxation is a common sequel of cervical spine involvement by rheumatoid arthritis. The incidence has been reported as being as high as 25% for anterior atlanto-axial subluxation (Conlon *et al.*, 1966) and 3.7% to 5% for vertical subluxation (Henderson, 1975; Mathews, 1976) while combinations of the two, causing a tilting, rotational luxation have been recently recognized (Eulderink and Meijers, 1976). Cases of posterior subluxation have been uncommon (Isdale and Corrigan, 1970; Verjaal and Harder, 1965). In an area so commonly affected by rheumatoid arthritis, it is surprising that lateral subluxation of the atlas is an infrequently recognized phenomenon. In this paper two patients are described who developed lateral subluxation of the atlas. This deformity was suspected on clinical

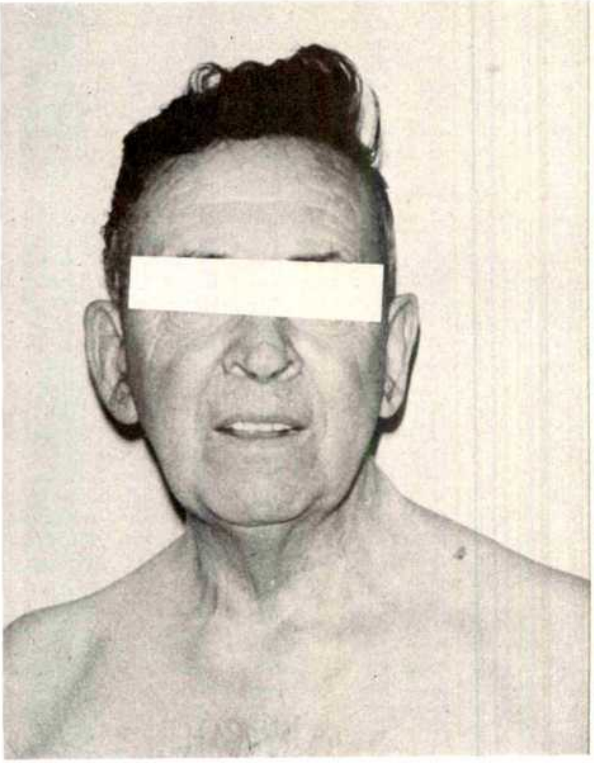


FIG. 1.

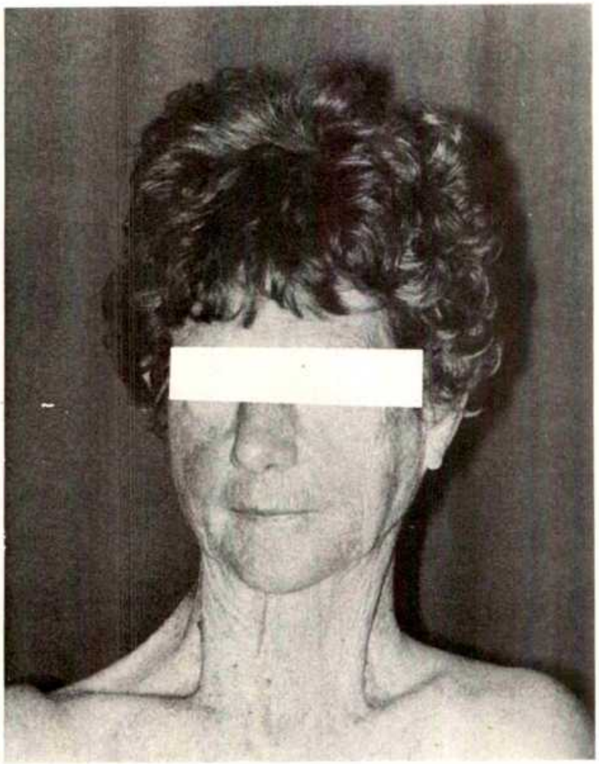


FIG. 2.

These clinical photographs show the characteristic posture of the head and neck acquired by both patients. In Fig. 1 (Case 1) note the scoliosis of the neck to the right and the reverse tilt of the head back towards the vertical. Fig. 2 (Case 2) demonstrates the scoliosis of the neck to the left and the reverse tilt of the head towards the midline.

Reprints: requests to D. G. Palmer.

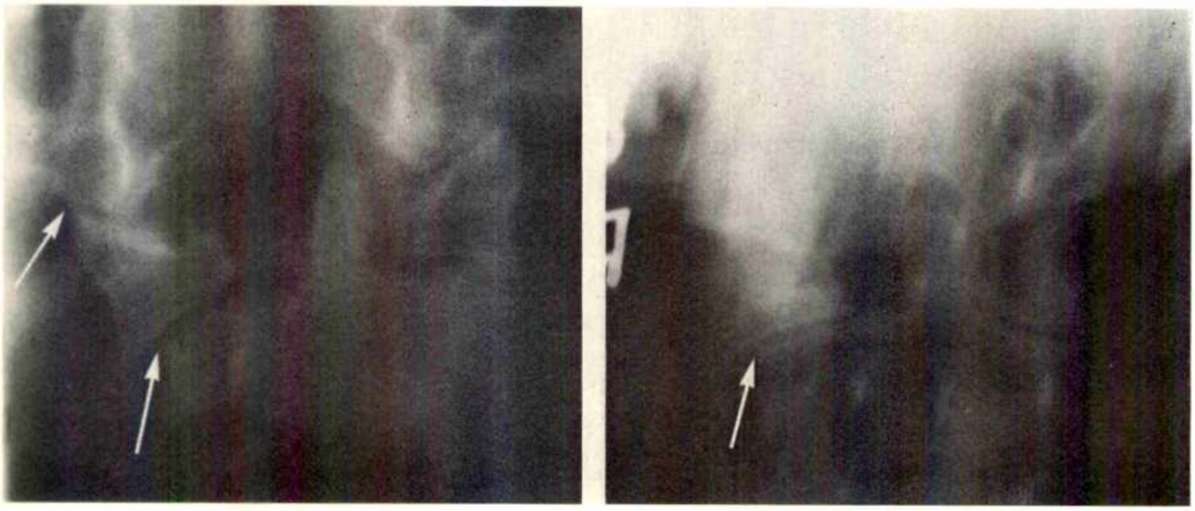


FIG. 3.

FIG. 4.

Tomography of the atlanto-axial region has demonstrated lateral subluxation of the atlas in respect to the axis (arrows) in both patients and in Case 1 (Fig. 3) the lateral shift of the occiput in respect to the atlas can be seen (arrow).

grounds and was confirmed by radiological examination.

CASE REPORTS

Both patients shared similarities in disease duration and in the severity of articular and extra-articular involvement.

Case 1

A 51-year-old European male developed a polyarthritis at 40 years of age. The disease ran a progressive course and he was admitted to hospital, eight years later (1974) for assessment. Examination showed severe generalized joint deformities associated with olecranon nodules, a sheep cell agglutinating titre for rheumatoid factor of 1:512 and radiological evidence of erosive changes in the small joints of the hands and feet particularly. An additional finding was advanced finger clubbing associated with the radiological changes of diffuse pulmonary fibrosis. The diffusing capacity for carbon monoxide was markedly impaired. A diagnosis of rheumatoid disease with pulmonary involvement was made. Evidence of an associated vasculitis later developed.

The patient was treated with soluble asprin and injections of gold sodium thiomalate with a good response. During the course of follow-up it became apparent that his head had developed a peculiar tilt. A scoliosis of the upper cervical spine to the right was present; but the head was tilted back towards the vertical with some deviation of the chin to the opposite side (Fig. 1). This gave the appearance of the head having been displaced towards the right shoulder. In July 1977, examination showed movement of the cervical spine to be limited. Rotation to the right was reduced to 30° and to the left 50° lateral bending was reduced to 20° bilaterally and flexion and extension were impaired. No sensory or motor changes were detected but the right Babinski response was up-going. There was no disturbance of bladder or bowel function.

Case 2

The second patient is a 68-year-old European woman who has similar severe erosive nodular rheumatoid disease of some 28 years' duration. Pulmonary involvement is not present, however, and no evidence of vasculitis has been noted. The sheep cell agglutinating test has been significantly elevated to a titre of 1:1024. The patient was treated with soluble asprin and injections of gold sodium thiomalate. While under periodic review it was noted that her neck had progressively developed a scoliosis to the left and the head a tilt back towards the vertical. As in the first patient, the appearance was that of the head having been shifted laterally towards one shoulder (Fig. 2). Examination of the movements of her cervical spine in July (1977) showed limited flexion and extension. Rotation to the right was reduced to 40° and to the left 45°. Lateral bending to the right was 0° and to the left 20° There were no signs of long tract or of bladder or bowel dysfunction and the Babinski responses were normal.

Radiological examination

In both cases lateral deviation of the atlas in respect to the axis was evident in the AP views of the cervical spine. Antero-posterior tomography (Figs. 3 and 4, 5 and 6) showed erosion of the internal surfaces of the lateral masses of the atlas and of the odontoid peg. There was narrowing and irregularity of the atlanto-axial joints. In the first patient there was bilateral atlanto-axial subluxation and right-sided atlanto-occipital subluxation both occurring in the horizontal plane. In the second case there was bilateral atlanto-axial subluxation in the horizontal plane with no evidence of an offset of the atlas in relation to the occipital condyles. Anterior subluxation of the atlas on the axis was present in the lateral view of the flexed neck in both cases (10 mm in Case 1, 5 mm in Case 2). It was of interest that initial tomography in the second patient failed to detect the lateral subluxation which had been shown in the plain film, because the abnormal posture had been corrected during the tomographic procedure (Fig. 7).

Dissection of the atlanto-axial complex

A dissection of the atlanto-occipital and atlanto-axial joints was undertaken on a formol-saline preserved specimen consisting of the base of the occiput and cervical spine removed at post-mortem from a 56-year-old male. The posterior arches of the atlas and axis were removed. The bed formed for the anterior aspect of the cervical cord by the posterior longitudinal ligament which anchors adjacent vertebrae and which expands above into the occipito-axial ligament was noted. This broad band of longitudinal fibres covers the odontoid process before attaching above to the anterior and lateral margins of the foramen magnum. An

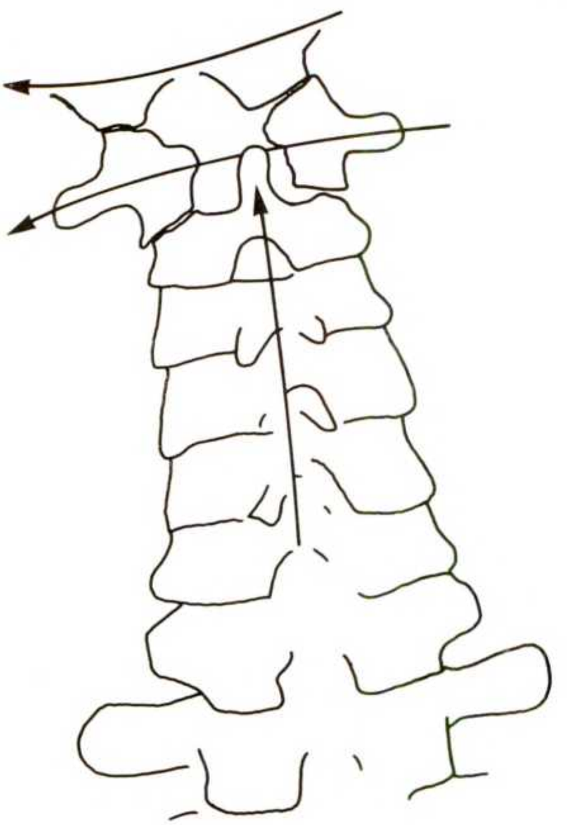


FIG. 5.

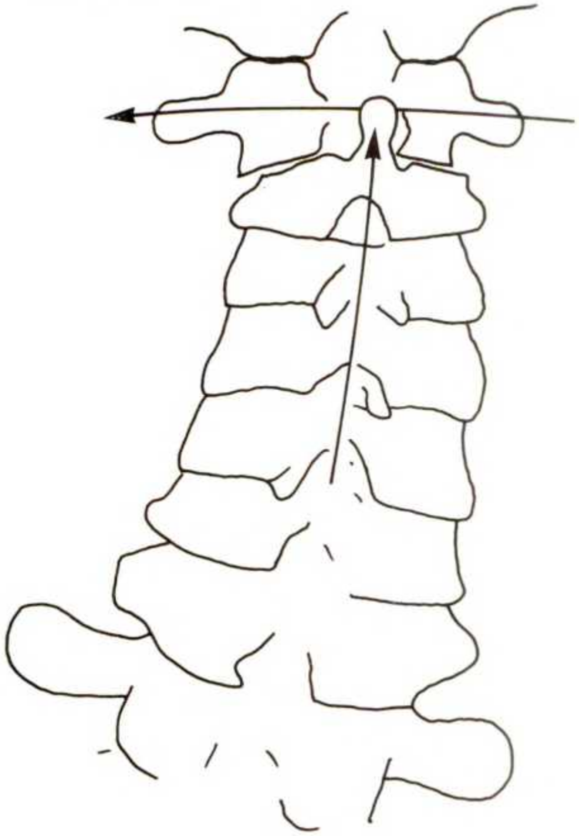


FIG. 6.

These sketches clarify the lateral shift of the axis in respect of the atlas and the mechanism by which the tilt of the head has been corrected—by subluxation at the atlanto-occipital joint (Case 1) and by a cervical scoliosis in the opposite direction to the shift (Case 2).

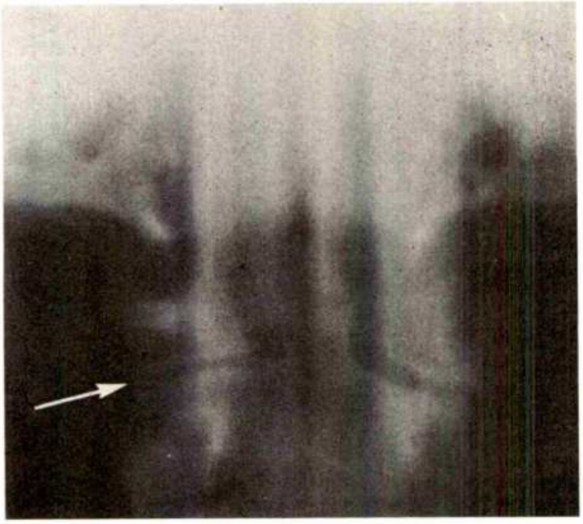


FIG. 7.

Case 2. Correction of the lateral subluxation of the atlanto-axial joint during initial tomography.

incision was made through this sheet of strong fibrous tissue and the transverso-dental joint entered. Probing demonstrated this to be a remarkably large cavity. The posterior longitudinal ligament and occipito-axial ligament were then split centrally in the coronal plane and one half dissected to reveal the broad underlying transverse ligament. The latter, attached to the odontoid in the mid-line, was noted to have an extensive attachment to the medial aspect of the corresponding articular mass of the atlas. The longitudinal fibres running between the occiput, odontoid and body of the axis, which complete the cruciate ligament were identified. Section of the transverse ligament and blunt dissection revealed the oblique fibres of the alar ligament running upwards and outwards from the odontoid to attach to the medial aspect of the foramen magnum (Fig. 6).

DISCUSSION

The cervical spine is a common area of involvement in rheumatoid arthritis, 50% to 80% of such patients showing radiological changes in this area (Conlon *et al.*, 1966; Bland *et al.*, 1963). These changes are osteoporosis, narrowing of the disc spaces, erosions and subluxation (Bland *et al.*, 1963; Isdale and Corrigan, 1970). From 16% to 25% of patients have subluxations at one or more levels

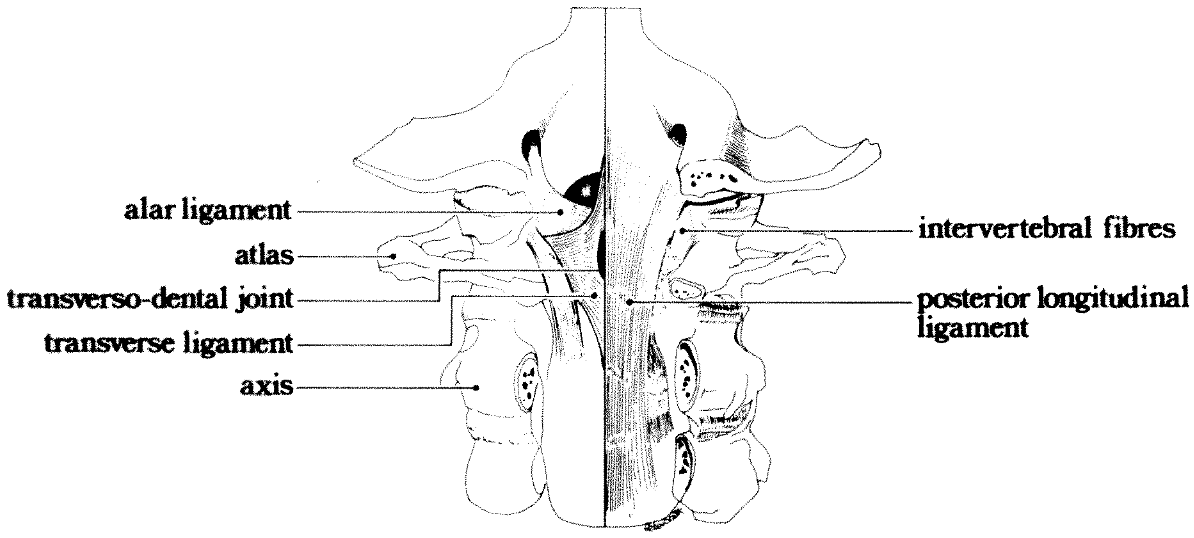


FIG. 8.

Stylized sketch of the ligaments of the upper cervical spine. Note particularly the deep intervertebral fibres of the posterior longitudinal ligament and the exposed transverse and alar ligaments.

(Conlon *et al.*, 1966; Smith *et al.*, 1972). The various changes in the cervical spine, especially anterior subluxation, are more prone to occur in those patients who are seropositive for rheumatoid factor (Eulderink and Meijers, 1976; Henderson, 1975; Smith *et al*, 1972).

The pathology resulting from rheumatoid involvement of this area has been described by Eulderink and Meijers (1976) as consisting of synovial inflammation and pannus formation with the destruction of bone and cartilage leading to loss of joint space. Occasionally bony ankylosis may occur.

The four diarthrodial joints through which the atlas articulates with the axis are as follows:

1. The atlanto-dental joint. This joint is interposed between the posterior aspect of the anterior arch of the atlas and the anterior aspect of the odontoid.
2. The transverso-dental joint. This joint lies between the transverse ligament and the posterior aspect of the odontoid.
3. The two joints between the lateral masses of the atlas and the axis.

The bone surfaces of the inferior articular facets of the atlas are concave in form, but the greater thickness centrally of the overlying cartilage converts these to being convex in shape. Furthermore the convexity of the superior articular facets of the axis is likewise increased (Coutts, 1934). Antero-posterior stability is thus entirely dependent upon the integrity of the capsular ligaments and associated accessory ligaments. The three occipito-odontoid ligaments also assist in maintaining the odontoid in position, especially the two strong alar ligaments which anchor the odontoid to the occiput (Adams and Schofield, 1965). All the joints of the atlanto-axial complex possess capsular ligaments but the synovial cavities of the four joints often intercommunicate according to Coutts (1934), and thus in certain individuals all might be expected to be concurrently involved by inflammatory disease.

Erosion of the medial aspects of the lateral masses of the atlas or of the odontoid peg with detachment of the transverse ligament and disruption of the deep fibres of the posterior longitudinal ligament would seem to be the principal factors which would lead to the development of lateral subluxation of the atlas on the axis. Lateral instability would be accentuated by damage to the capsular ligaments of the lateral atlanto-axial joints. Damage to the occipito-odontoid ligaments (alar ligaments) and the occipito-axial ligament would allow movement of the axis to occur independently of the occiput.

This pattern of damage, primarily involving the transverse ligament, would inevitably result in concurrent anterior subluxation of the atlas. This association was present in both of our patients. In contrast, anterior subluxation of the atlas usually occurs independently of lateral subluxation. We believe that this observation reflects the fact that the posterior longitudinal ligament need not be disrupted for anterior subluxation to occur. If, however, the deeper fibres of this ligament uniting the adjacent vertebrae were to be detached, then additional lateral instability would result.

The lateral shift of the head towards one shoulder with the secondary tilt of the head back towards the vertical produced the rather characteristic posture observed in both patients. In the first case the scoliosis of the cervical spine was in the same direction as the lateral shift of the atlas on the axis and the secondary restoration of the head towards the vertical was due to additional subluxation at the atlanto-occipital joint. In the second case the lateral tilt of the head from the atlanto-axial subluxation was corrected by the development of a cervical scoliosis in the opposite direction.

It has been demonstrated radiologically in normal subjects (Hohl, *et al.*, 1964; Jirout, 1973) that some lateral displacement of the atlas on the axis may commonly be noted when the neck is laterally flexed beyond 15°. The pathological nature of the shift noted in our two patients was reflected in the displacement being associated with an acquired abnormality of cervico-occipital posture.

In the second patient it was possible to correct the radiological appearances of lateral subluxation almost fully by tilting the head to the opposite side. Thus the radiological diagnosis of lateral subluxation of the atlas may be missed if the deformity is corrected during radiological examination. It is also quite possible that lateral subluxation would be more commonly found if antero-posterior views were to be taken with the head flexed to either side when the diagnosis is suspected. This situation is, of course, analogous to the flexion and extension views required when radiological evidence of anterior subluxation is sought.

Neurological signs are not commonly associated with anterior subluxation in contrast to vertical subluxation where cord damage is common and cases of sudden death have been reported (Swinson, *et al.*, 1972; Henderson, 1975; Mathews, 1976; Mikulowski, *et al.*, 1975). It may be of significance that in our experience of just two patients, one did have evidence of upper motor neurone damage which does perhaps suggest that lateral subluxation of the atlas on the axis may also prove to have a significant association with cord damage.

ACKNOWLEDGMENTS

The financial support of the Medical Research Council of New Zealand is gratefully acknowledged. Mr. P. Scott produced the sketches and reproduction of the X rays was undertaken by Mr. B. P. O'Connor.

REFERENCES

ADAMS, W. E., and SCHOFIELD, G. C., 1965. *Manual of Human Anatomy*, 1st edn., pp. 405–411 (N. M. Peryer Ltd, Christchurch, New Zealand).

BLAND, J. H., DAVIS, P. H., LONDON, M. G., VAN BUSKIRK, F. W., DURANTE, C. G., and BURLINGTON, V. T., 1963. Rheumatoid arthritis of cervical spine. *Archives of Internal Medicine, 112.* 892–898.

CONLON, P. W, ISDALE, I. C., and ROSE, B. S., 1966. Rheumatoid arthritis of the cervical spine. An analysis of 333 cases. *Annals of the Rheumatic Diseases, 25,* 120–126.

COUTTS, M. B., 1934. Atlanto-epistropheal subluxations. *Archives of Surgery, 29,* 297–311.

EULDERINK, F., and MEIJERS, K. A., 1976. Pathology of the cervical spine in rheumatoid arthritis: a controlled study of 44 spines. *Journal of Pathology, 120,* 91–108.

HENDERSON, D. R. F., 1975. Vertical atlanto-axial subluxation in rheumatoid arthritis. *Rheumatology and Rehabilitation, 14,* 31–38.

HOHL, M., BAKER, H. R., and HILLS, B., 1964. The atlanto-axial joint. *Journal of Bone and Joint Surgery, 46A,* 1739–1752.

ISDALE, I. C., and CORRIGAN, A. B., 1970. Backward luxation of the atlas—two cases of an uncommon condition. *Annals of the Rheumatic Diseases, 29,* 6–9.

JIROUT, J., 1973. Changes in the atlas-axis relations on lateral flexion of the head and neck. *Neuroradiology, 6,* 215–218.

MATHEWS, J. A., 1976. Rheumatoid atlanto-axial subluxation *British Medical Journal, 2,* 638–639.

MIKULOWSKI, P., WOLLHEIM, F. A., ROTMIL, P., and OLSEN, I., 1975. Sudden death in rheumatoid arthritis with atlanto-axial dislocation. *Acta medica Scandinavica, 198,* 445–451.

SMITH, P. H., BENN, R. T., and SHARP, J., 1972. Natural history of rheumatoid cervical luxations. *Annals of the Rheumatic Diseases, 31,* 431–439.

SWINSON, D. R., HAMILTON, E. B. D., MATHEWS, J. A., and YATES, D. A. H., 1972. Vertical subluxation of the axis in rheumatoid arthritis. *Annals of the Rheumatic Diseases, 31,* 359–363.

VERJAAL, A., and HARDER, N. C., 1965. Backward luxation of the atlas. *Acta Radiologica Diagnostica, 3,* 173–176.

1978, *British Journal of Radiology*, *51*, 968–973

A comparison of grey-scale image recording systems

By Hylton B. Meire, F.R.C.R. and Pat Farrant, D.C.R.M.U.

Ultrasound Section, Division of Radiology, Clinical Research Centre and Northwick Park Hospital, Harrow

(*Received April, 1978 and in revised form July, 1978*)

ABSTRACT

There is currently a rapid rise in the variety of image recording systems and recording media available for use with ultrasound and CT scanners. We have evaluated nine different systems and ten recording media and have compared their cost, convenience and performance.

The choice of system in a particular department depends upon many factors, especially the number of images recorded and the reasons for recording them. We suggest that a busy department will probably require one of the more expensive automatic devices since these are the most convenient to use and have the lowest cost per image.

Coincident with the rapid proliferation of grey-scale ultrasound equipment and computerized X-ray scanners there has been an increase in the variety of image-recording systems. The capital cost, running cost and performance of the currently available systems vary widely, several being both expensive and inadequate.

In order to assist those faced with the decision as to which system suits their needs best, we have compared a wide range of devices and recording media.

The exact requirements of the system used in any one institution may be very different from those in another depending, to a great extent, on the number of images taken per year, the availability of a suitable photographic processor and the reason for which the image has been recorded. Most commonly the record is used either as the medium from which the diagnosis is made or as a record for comparison with any future scans. In the UK the majority of institutions record their images only for the latter, archival, purposes.

We have evaluated nine different commercially available recording systems (Table I), ten different recording media (Table II), and have compared a wide range of factors for each combination (Table III).

First, we will describe the recording systems and their capital costs and then discuss the different recording media and their cost for each exposure. We will then discuss the other factors listed in Table III.

RECORDING SYSTEMS

35 mm camera

The standard single lens reflex camera back can be mounted on a special adaptor and fitted with a close-up lens to permit direct recording from a TV monitor. We have evaluated a manually operated version, though automatic electrically driven 35 mm cameras are available.

70 mm camera

The Polaroid back for the standard oscilloscope camera can be replaced by a special back which accepts a 70 mm film magazine. The lens and oscilloscope mountings remain unchanged. The version we have studied is manufactured by Shackman,* is manually operated and holds sufficient film for 50–60 images. A version with electrically operated shutter and automatic electric film advance is available (in the USA) but is very much more expensive.

Multiformat camera

The manually operated versions of this consist of a special cassette which houses an X-ray type film (commonly 10 × 8 inch, *i.e.* 250 × 200 mm film). The cassette and housing fit onto the standard oscilloscope camera in place of the Polaroid back. In use the cassette has to be repositioned by hand into one of nine different positions after each exposure, thus resulting in nine separate images on one film (versions are available with different film sizes and different numbers of images per film).

The automatic multiformat cameras are entirely self-contained with an integral monitor. The images are positioned automatically on the film in a predetermined sequence and exposure is effected merely by depressing a remote button. Numerous combinations of film size and number of images per film are available.

Polaroid camera (oscilloscope mounted)

This is the standard Shackman camera usually offered by ultrasound equipment suppliers in the UK. It is normally mounted on a dedicated slave monitor and has a manually operated shutter.

Polaroid camera (hand held)

The Polaroid CR9 camera is a simple moulded-plastic, fixed focus camera for recording oscilloscope images. We have evaluated its performance as a means of recording grey-scale TV images. Although it was not intended for this purpose several institutions make use of it as it is the cheapest available oscilloscope camera.

---

* Shackman Instruments Ltd., Mineral Lane, Chesham, Bucks HP5 1NU.

Video hard copier

This device produces fully developed finished positive or negative prints of stationary TV images within fifteen seconds. The images are very large (about 17 × 22 cm typically) and the image magnification factor can be varied by ±25%. The unit is entirely self-contained requiring no additional monitor, developer, etc. The one evaluated was the Tektronix 4632.*

Bromide paper roll camera

These devices are a fairly new innovation, the one evaluated was the Tudorcape† "Vidicam". This system is also self-contained including a high definition TV monitor and automatic advance after each exposure. Stationary TV images are recorded onto bromide photographic paper, the exposed paper being stored in a cassette. The cassette has to be removed from the machine and taken to a suitable photographic processor for development. Three different image sizes are available and images can be either positive or negative.

Capital Cost

(As at November, 1977) (Table I)

35 mm camera

For this system one requires a special oscilloscope mounting, 35 mm camera adaptor flange, close-up lens and camera body. Using a Praktica camera back and Shackman components we assembled our system for about £750. With a little ingenuity it could probably be done by a hospital physics department for a lot less.

TABLE I

Recording systems	Capital cost (see text) (as at Nov. 1977)
	£
35 mm camera	750
70 mm manually operated camera	1050
70 mm automatic camera	3000+
Multiformat manually operated camera	800–1500
Multiformat automatic camera	4000–8000+
Polaroid oscilloscope mounted camera	590
Polaroid hand held camera	75
Video hard copier	3000
Bromide paper roll camera	2700

70 mm manual camera

The 70 mm camera back and magazine to adapt the Polaroid system for 70 mm use raises the cost of this unit to £1050. In addition, at least one extra magazine will be required (for use while exposed film is being developed) and this will add a further £300.

70 mm automatic camera

This device was used and evaluated in the USA. Electrically driven 70 mm magazines are available in the UK but would raise the cost of the camera to over £3000.

Multiformat camera back (manually operated)

Several makes are available and all fit the standard Shackman oscilloscope camera. Prices vary from £300 to over £800 for supply direct from the manufacturer and, as with other cameras, it will be more expensive if supplied through the scanner equipment manufacturers.

Multiformat automatic cameras

There is also a fairly wide choice of these. The most basic version costs around £4000 while the more sophisticated and versatile varieties are priced at well over £8000.

Polaroid oscilloscope mounted camera

The standard Shackman camera costs £590 when supplied through the ultrasound equipment manufacturer. We found that we had to buy the whole of this unit even if we only required the mounting and lens for use with a 70 mm back.

Polaroid hand held camera

The CR9 camera was available in 1977 for £75 and has the lowest capital cost of all the systems we have evaluated.

Video hard copier

Our unit was supplied three years ago by the scanner manufacturer. It is no longer available through them and we have been quoted a price of £3000 for supply direct from the manufacturer.

Bromide paper roll camera

This was purchased direct from the manufacturer at a price of £2700 in late 1977.

The 35 mm, 70 mm, manual multiformat and Polaroid cameras all require a separate slave monitor at a cost of about £250.

---

*Tektronix (U.K.) Ltd., 36 Coldharbour Lane, Harpenden, Herts AR5 4VP.

†Tudorcape Ltd., 28 Southwood Lane, London, N.6.

TABLE II

Recording media	Cost per exposure (pence) (Nov. 1977)	Image size (mm)
35 mm negative film (Ilford FP4)	1.6	24 × 35
35 mm positive film (Agfa Dia-Direct)	3.0	24 × 35
35 mm positive film (Kodak SO 185)	2.6	24 × 35
70 mm negative film (Kodak RAR)	3.0	55 × 70
70 mm negative film (Kodak RPF)	3.0	55 × 70
Multiformat (nine images on a 10 × 8 inch (250 × 200 mm) film)	4.0	57 × 80
Polaroid 107C	29.1	73 × 95
Video hard copy paper	10.0	170 × 220 ±25%
Bromide paper (Ilford "Ilfospeed")		
Vidicam large print	4.2	135 × 165
Vidicam medium print	2.8	100 × 140
Vidicam small print	2.0	85 × 120
Experimental Ilford film for Vidicam	paper cost × 4	as per paper

Recording Media

These are listed in Table II.

The 35 mm negative film is the standard film used for general black and white photography.

The 35 mm positive films are commercially available. The Agfa-Gevaert Dia-Direct has an ASA rating of 32 permitting exposure times of ½ to 1 second but has to be returned to the manufacturers for processing. The Kodak rapid processing film is very slow indeed, requiring about 30 seconds per exposure, but can be processed through an X-ray film processor.

The 70 mm films are both standard X-ray fluoroscopic films. They are sufficiently fast to permit short exposures and can be rapidly processed. RAR has a wider exposure latitude and better grey-scale than RPF. Suitable films are also made by several other manufacturers though we have not tested the whole range.

Multi-imager films. Ordinary X-ray film is too fast and has too high a contrast for this purpose. Special films are made by the major film manufacturers and are very satisfactory in terms of speed, resolution and grey scale. They are processed through a conventional X-ray film processor.

Polaroid. We have used type 107C film which does not require coating after exposure. It has a very fast speed, high contrast and narrow exposure latitude.

The video hard copiers require special "dry silver" photographic paper which is made especially for this purpose. It is supplied in large cassettes which hold sufficient for over 500 exposures. This paper has a "shelf life" of a few months.

TABLE III

Factors compared

Capital cost
Cost per exposure
Convenience
Grey-scale capability
Image permanence
Reliability
Special uses

The bromide paper roll camera uses standard resin coated photographic paper (Kodak "Veribrom" or Ilford "Ilfospeed"). The Vidicam holds sufficient paper to give 800 large prints or 1200 of the small format. The paper can be processed manually or through an X-ray film processor.

An experimental film material produced by Ilford has also been used in our Vidicam. It is handled and processed in the same manner as the paper and the unit can be set to give either positive or negative images as required. The cost will probably be about four times that of the resin coated paper.

Cost per Image

These are also shown in Table II. Costs fall into four groups:

(a) less than 2p.
35 mm negative film
(b) 2–4p.
35 mm positive film;
70 mm films;
Multiformat images;
Vidicam prints
(These costs assume the availability of an existing film processor. Its capital cost and the small

TABLE IV

CONVENIENCE

	Per exposure	Processing	Viewing	Storage	Image identification
35 mm manual negative	+	−	−	−	−
35 mm manual positive (Dia-Direct)	+	− −			
(Kodak S0185)	− −				
70 mm manual	+	−	+	−	−
70 mm automatic	+ +				−
Multiformat manual	−	−	+	+ +	−
Multiformat automatic	+ +				−
Polaroid	−	+	+	+	− −
Hard copier	+	+ +	+ +	+	− −
Vidicam print	+ +	−	+ +	+ +	−
Vidicam film			+		−

additional quantities of chemicals used have not been included in the costings.)

(c) 10p.
Video hard copier

(d) 30p.
Polaroid

Other factors to be compared below are listed in Table III.

CONVENIENCE

We have subdivided the convenience of usage for each system into five groups (Table IV) which represent the most important factors concerning the scanner operator, the radiologist and the clerical and secretarial staff. Each is discussed in brief below.

Exposure

The least convenient systems require long exposure times or multiple manual manoeuvres for each exposure. If large numbers of images are recorded this can become very important. The most convenient systems are the totally automatic ones.

Processing

The video hard copier processes its own films and is the most convenient in this respect. Polaroid images are also rapidly available and this is their major advantage. All other materials have to be processed remotely with consequent delay, though this is worst for the Dia-Direct which must be returned to the manufacturer for processing.

Viewing

Two factors are important here, image size and the need for viewing aids. The 35 mm films are small and need both illumination and magnification. The 70 mm and multiformat images are large enough to be viewed without magnification though they do require transillumination. The large prints from the video hard copier and Vidicam were judged easiest to view.

Storage

All images must be stored and the preferred method of storage appears to be in flat envelopes. The small roll films have to be cut and laminated into plastic sheets to be easily stored, and this extra step is time-consuming, expensive and inconvenient. The larger, stiffer images of the multiformat cameras and Vidicam are easiest to store.

Image identification

There are very many different methods for identifying images and we cannot discuss all of them. However, it is easier to add some form of identification to certain media than to others. The patient's name and other data can be recorded on any form of image if an electronic character generator is attached to the scanner. As an add-on unit these cost £850 to £1700 and many ultrasound machines currently in use do not have this facility. Under these circumstances some alternative means of identification has to be employed. This is rather difficult with the small format 35 mm films, though wax pencil can be used to write essential information on all types of film image. The Vidicam, Polaroid and hard copy prints are more convenient since a larger quantity of information can be written more easily on their reverse sides. The delay introduced by remote processing of the Vidicam and film images may increase the chance of error in identification. A conventional X-ray film actinic marker can be used to enter name and date on the multiformat images while certain makes of recording system include some form of integral image-labelling device. We have not evaluated these.

GREY-SCALE CAPABILITY

Since we are discussing the recording of grey-scale images the ability of each medium to record all the grey-scale information is most important. There are substantial differences between the capabilities of the various systems and we have therefore only judged them subjectively (Table V).

The 35 mm, 70 mm and multiformat film images are capable of recording the full range of grey-scale tones, though these may not be appreciated unless viewed under ideal conditions. In practice these films are frequently "held up to the light" for viewing and it is likely that only about four shades can be detected under these conditions.

Prints have inherently fewer shades of grey than transilluminated images. The Vidicam prints are markedly better than Polaroid, however, while the hard-copy images show very poor tonal range.

IMAGE PERMANENCE

The majority of images are recorded for archival purposes and therefore are expected to last many years. If stored in light-tight envelopes all the media we have used show no significant deterioration after three years. Permanence will be reduced, however, if Polaroid or hard copy images are left in bright light. The permanence of Polaroid 107C film seems to vary from pack to pack and severe degradation has been noted after about one year when exposed to normal room lighting. Hard copy images can be destroyed in a few days if left where sunlight may fall on them.

TABLE V

GREY-SCALE CAPABILITY

35 mm	+ +
70 mm RAR	+ +
Multiformat	+ +
Polaroid	+
Hard copier	—
Vidicam	+ +

TABLE VI

RELIABILITY

35 mm	+ +
70 mm	+
Multiformat manual	+
Multiformat automatic	+ +
Polaroid (Shackman)	+
Polaroid (CR9)	—
Hard copier	—
Vidicam	+

RELIABILITY

The reliability of each recording system has been assessed based upon our own experience over nearly three years with most systems and by obtaining opinions from other users. Our findings are summarized in Table VI.

The 35 mm and automatic multiformat cameras appear to be generally reliable. Many users have had recurrent mechanical problems with the 70 mm magazines.

The manually operated multiformat cameras are somewhat variable in reliability, the cheaper versions often suffering from failure of the catches which ensure correct positioning of the images.

The Shackman Polaroid oscilloscope camera has proved reliable provided the spreader rollers are cleaned regularly, while the CR9 camera has suffered failure of almost every component—especially the spreader—and film wastage has often exceeded 10%. We understand that this camera is no longer available and is being replaced by a more robust version. At the time of writing, however, we still find it available for sale.

The video hard copier has also proved unreliable both with mechanical failures in the transport and guillotine systems and with fairly rapid deterioration of the integral cathode-ray tube. This system is no longer offered as an option with ultrasound scanners in the UK.

The Vidicam has not been available for long enough for its reliability to be assessed. Early versions have had some trouble with the paper transport mechanism. After modification to the receiving cassette our Vidicam has run well for six months to date.

Special uses

In addition to archival use scanner images may be recorded for other specialized purposes and certain recording media are most suited to some of these. We have summarized our impressions in Table VII.

We have found the large hard copy images especially valuable for measurement of fetal crown rump length, abdominal circumference, etc., and the

TABLE VII

SPECIAL USES

35 mm:	lectures and publications
Polaroid:	where a few "instant" images are felt necessary
Hard copy:	large images for measurement (see text)
Vidicam:	publications

TABLE VIII

FILM COST PER 10000 IMAGES

	£
35 mm negative	160
35 mm positive	3–400
70 mm	
Multiformat	
Vidicam print	
Polaroid	3000

copier can be adjusted to give exactly life-size images, thus avoiding the need for applying correction factors.

The Vidicam images are glossy bromide prints which are suitable for direct submission with scientific papers.

CONCLUSIONS

We regard the 35 mm images as being too small for routine work. The video hard-copy images have inadequate grey scale for faithful reproduction of non-obstetric ultrasound scans and the equipment has proved unacceptably unreliable.

Polaroid film is far too expensive to be used for recording all images in a busy department and we have found it very messy when used in large quantities. Its narrow exposure latitude ensures that one seldom obtains optimum results.

For those users who require a transparency image the 70 mm or multiformat images would seem to be ideal whereas the Vidicam prints are similar in price and are easy to view and store. A very busy department would probably prefer the automatic multi-imager or Vidicam as these are simpler to use.

We regard the running costs of a system to be at least as important as its capital cost and have compared the running costs of each system per 10000 exposures per year (Table VIII). In our department in 1977 we recorded 75000 images on 70 mm film at a cost of about £2000. If Polaroid were used it would have cost £22500.

Book review

An atlas of normal developmental roentgen anatomy. By T. E. Keats and T. H. Smith, pp. x+801, illus., 1977 (Year Book Medical Publishers, Inc. Chicago and London) £53·00.

This atlas consists of series of radiographs of males and females from birth to twenty-five years of age. The only annotation is the sex and age of child on each page.

For the first two years the age intervals are three months; from two years to twenty-five years, yearly intervals are chosen.

Each age group starts with an extensive skeletal survey. Then there are films of the upper respiratory passages and chest. Abdomen, supine and erect, precedes barium swallow, meal and follow-through, then enema with bowel filled with barium and after evacuation. A single full length intravenous urogram is followed by cystograms with the bladder at various stages of filling and emptying. A cholecystogram finishes off most series from four years onwards and a single operative cholangiogram at three months is included.

The volume is large, well bound and beautifully illustrated but expensive because of the high quality of radiograph reproduction.

It is intended as a convenient alternative to a "normal film" museum which takes so much time and effort to collect and further effort to use. It serves its purpose well but seems unnecessarily long. Two yearly intervals would surely be adequate after twelve years of age? The skeletal section is particularly valuable and might be further enhanced—for example by a basal view of the skull. The barium studies and cholecystograms are of questionable value and the inclusion of so many uninformative bladder films seems unnecessary.

In spite of these criticisms this volume can be recommended as a useful addition to departmental libraries. It is pleasant and rewarding to use. As its use requires less effort than a "normal film" museum, it will commend itself to busy radiologists.

ELIZABETH M. SWEET.

1978, *British Journal of Radiology*, *51*, 974–980

Reduction of radiation dose to patients in xeroradiography

By T. H. E. Bryant, B.Sc. and W. L. Julian, M.Sc.

Department of Physics as Applied to Medicine, The Middlesex Hospital Medical School, Cleveland Street, London W1P 6DB

(*Received July, 1977 and in revised form December, 1977*)

ABSTRACT

A method for reducing the radiation dose received by the patient in xeroradiography is described. It is shown, theoretically, that a dose reduction of about 50% can be achieved, and measurements of skin exposure confirm reductions of this order. There is no appreciable loss of image quality, and the theory suggests that it may even be possible to enhance the visualization of soft tissue by this method.

Xeroradiography is an increasingly popular method of producing a radiographic image in which the conventional film is replaced by a selenium-coated plate. The image is formed by an electrostatic process, followed by powder-cloud development (Boag, 1973). Advantages of the method include visualization of fine detail due to "edge contrast enhancement" and a wide recording latitude making it possible to visualize detail of bone and soft tissue in the same image. It has been found that when manual processing is used, the skin exposure to the patient is of the same order as that delivered in conventional radiography with film (Boag *et al.*, 1976). However, using the automatic processing equipment currently available and the exposure conditions recommended by the manufacturers, production of a xerogram of good diagnostic quality results in a much higher radiation dose to the patient than that necessary for conventional radiography (the field of mammography is a special case and is not discussed here). This report describes how it is possible to reduce this radiation dose considerably by filtration of the X-ray beam and discusses the effect of this on image quality.

METHODS OF REDUCING RADIATION DOSE

There are three possible methods by which the radiation dose received by the patient could be reduced:

(i) increase of plate sensitivity
(ii) increase of the X-ray tube voltage
(iii) modification of the X-ray spectrum to "match" the spectral sensitivity of the selenium plate.

Method (i) is in the hands of the manufacturer and, so far, plates of higher sensitivity have not been available.

Concerning method (ii), Fig. 1 shows how the measured incident exposure necessary for production of a xerogram of the neck decreases as the tube voltage is increased from 90 kVp to 140 kVp; the exposures were measured with an ionization chamber. The reason for the decrease is illustrated in Fig. 2 which shows how the sensitivity of the plates commercially available varies with the effective energy of the X-ray beam and that the plate is most sensitive at about 53 keV (Boag, 1973). Increase of the tube voltage leads to a high proportion of X-rays with this energy. However, in many X-ray departments the maximum tube voltage available is 120 kVp which means that, for routine use, this method of dose reduction is limited.

Method (iii), on the other hand, can be applied with little or no modification to existing equipment. The spectral distribution of 100 kVp X-radiation from a typical tungsten-target tube is shown in Fig. 3 (Atkins *et al.*, 1975) together with the spectra incident on the plate after passing through 5 cm muscle or 3 cm muscle overlying 2 cm bone, these being calculated from the original spectrum (see Appendix 1). From this, it is apparent that not only is the low-energy radiation wasted because the plate is comparatively insensitive to it, as shown in Fig. 2, but much of it fails to reach the plate because it is absorbed by the patient.

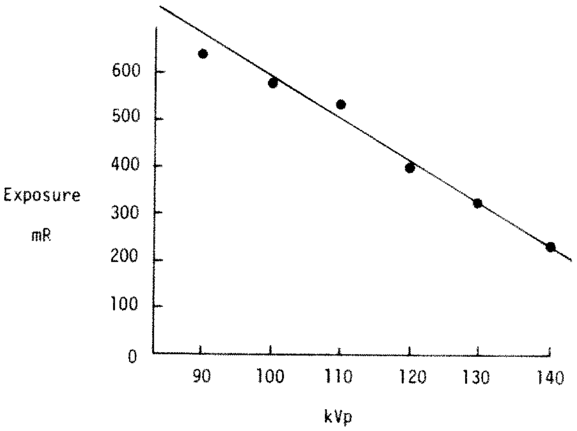


FIG. 1.

Variation with kVp of measured incident exposure, for a xerogram of the neck.

One way of reducing the amount of low energy radiation present is by the use of filtration. Figure 4 shows the same 100 kVp spectrum together with spectra produced by passing it through copper filters of three different thicknesses (once again calculated from the original spectrum). The low energy radiation which is most easily absorbed by the patient and therefore contributes considerably to absorbed dose is greatly reduced, while the higher energy radiation to which the plate is more sensitive is reduced comparatively little. Moreover, Fig. 5 shows two radiographs of the same specimen taken with the same exposure settings and in exactly the same conditions except that in the case of Fig. 5B, the beam was filtered with 0.15 mm copper. These two radiographs have been shown to eight radiologists and all agree that they are almost indistinguishable. The exposure measured with an ionization chamber at the position occupied by the specimen was 430 mR for Fig. 5a and 200 mR for Fig. 5B.

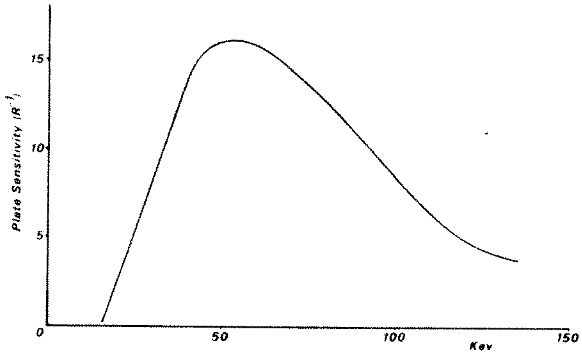


FIG. 2.
Sensitivity of selenium plates of thickness 130 μm as a function of X-ray energy (Boag, 1973).

USE OF COPPER FILTRATION

Effect on picture quality

To examine more thoroughly the effect of copper filtration on the quality of xeroradiographs, a set of 56 xerograms of the same specimen leg were made, with different combinations of filter thickness and exposure time: all other factors, *i.e.* kVp, mA, distance and processing conditions, were kept

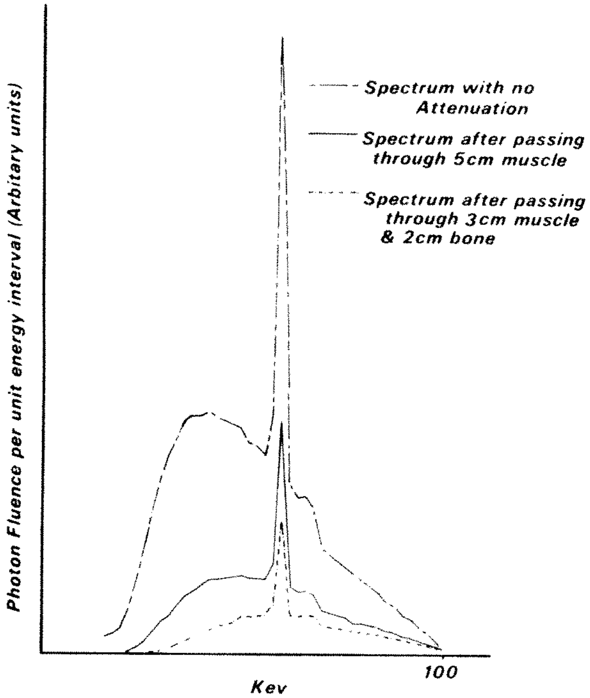


FIG. 3.
The spectral distribution of 100 kVp X-radiation from a typical tungsten-target tube with a total filtration of 2.7 mm aluminium equivalent (Atkins, *et al.*, 1975) and spectra produced by passing this radiation through 5 cm muscle or 3 cm muscle overlying 2 cm bone (linear co-ordinates).

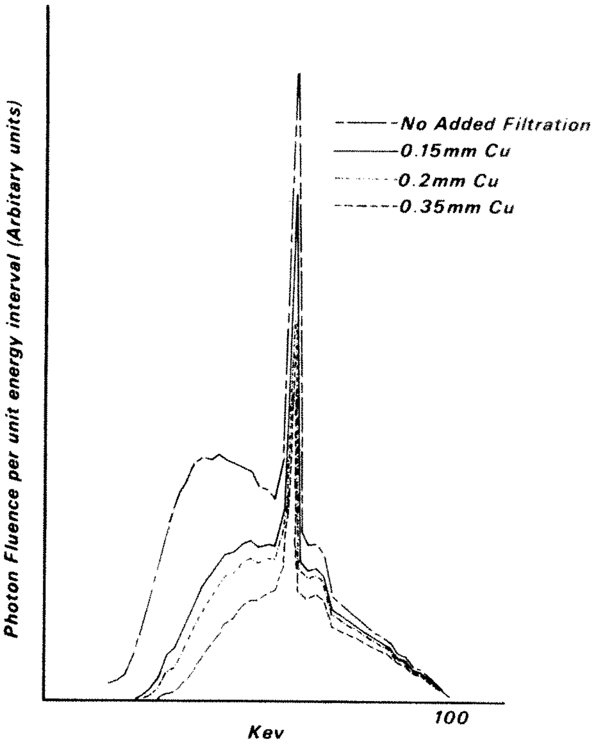


FIG. 4.
The spectrum of 100 kVp X-radiation and those produced by passing through copper filters of three different thicknesses (linear co-ordinates).

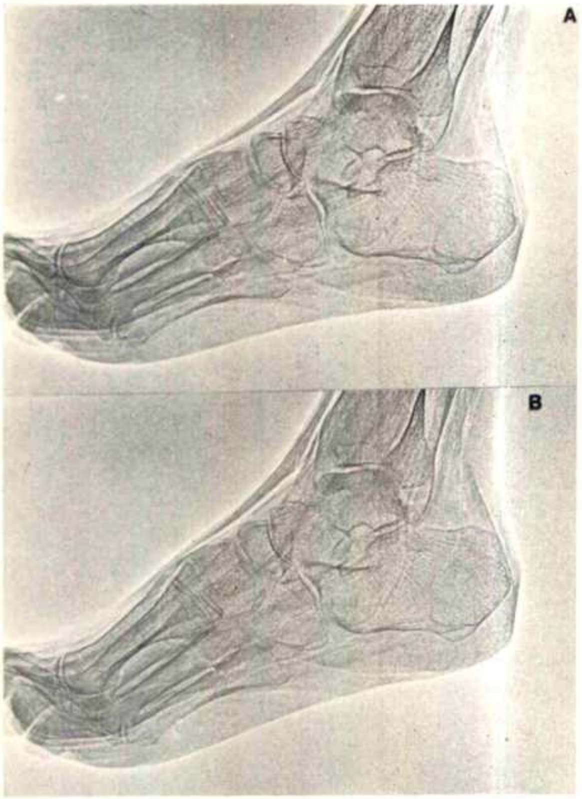


Fig. 5.

Xerograms of an embalmed foot using the same exposure settings and processing conditions, (A) with no added filtration (B) with 0.15 mm copper filter.

constant. The exposure time ranged from 4 mAs to 160 mAs for each filter thickness. The xerograms were then shown to a total of 24 radiologically trained observers who were asked to divide the set into two groups: those they would accept as good enough for diagnosis and those they would reject. They were also asked to pay particular attention to radiographic detail and to reject all xerograms with insufficient detail in either bone or soft tissue areas.

The results are presented as histograms in Fig. 6. The filter thicknesses used were 0.15, 0.2 and 0.35 mm (the only ones readily available). The total number of xerograms considered "acceptable" is seen to decrease as the filter thickness increases although this decrease is small for all but the thickest filter. This indicates, of course, that a small amount of detail has been lost but, as was illustrated in Fig. 5, the loss may be minimized by correct choice of exposure factors.

The reason for the change of image quality lies in the altered spectral distribution produced by filtration (see Fig. 4). Using this and the plate sensitivity curve of Fig. 2, it is possible to calculate what percentage of the original charge present on the plate will remain after a typical exposure (see Appendix 2). Figure 7 shows the percentage charge remaining on three different areas (an area of background, an area under 5 cm muscle and an area under 3 cm muscle overlying 2 cm bone) for the exposure factors used for the xerograms of Fig. 5.

Because filtration reduces the total exposure at any given setting of the X-ray set, more charge remains on all areas of the plate when the filter is used. However, because the development principle is based on the formation of "edges" rather than density differences, it is the difference in charge or the "charge step" between two areas which has a greater effect on picture quality than the absolute charge remaining on the two areas. It is this difference which also determines the actual "edge width" visible in the final image. In this example (Fig. 7), the change in size of the charge step is small: step (1), between background and muscle, changes from 31% to 36%; while step (2), between muscle and bone-and-muscle, changes from 27% to 21%. These tissue thicknesses are approximately the same as those present in the specimen of Fig. 5 and it can be seen that such a small change in size of step has virtually no effect on picture quality.

The fact that the size of step (1) increases and of step (2) decreases, leading to corresponding changes in the edge widths, suggests, however, that by an extension of the same method it may be possible to enhance the visualization of soft tissue against background, at the same time decreasing the clarity of bone which may be obscuring underlying tissue. To illustrate this, Fig. 8 shows how the calculated edge widths (Appendix 3) vary with exposure for both filtered and unfiltered beams. For both edges there is a "crossover point" at which the filtered and unfiltered beam will each give the same edge width. For exposures lower than this, addition of filtration reduces edge width while for exposures above this, addition of filtration increases edge width. The crossover point for edge (1) (muscle to background) is at a considerably lower exposure than that for edge (2) (bone to muscle). Therefore, for an exposure between these two limits, addition of filtration increases apparent "contrast" between muscle and background and decreases apparent "contrast" between muscle and bone. This, moreover, implies that there is also an exposure range for which addition of filtration enhances visualization of airways in soft tissue and also makes them more visible "through" bone. This has been confirmed in

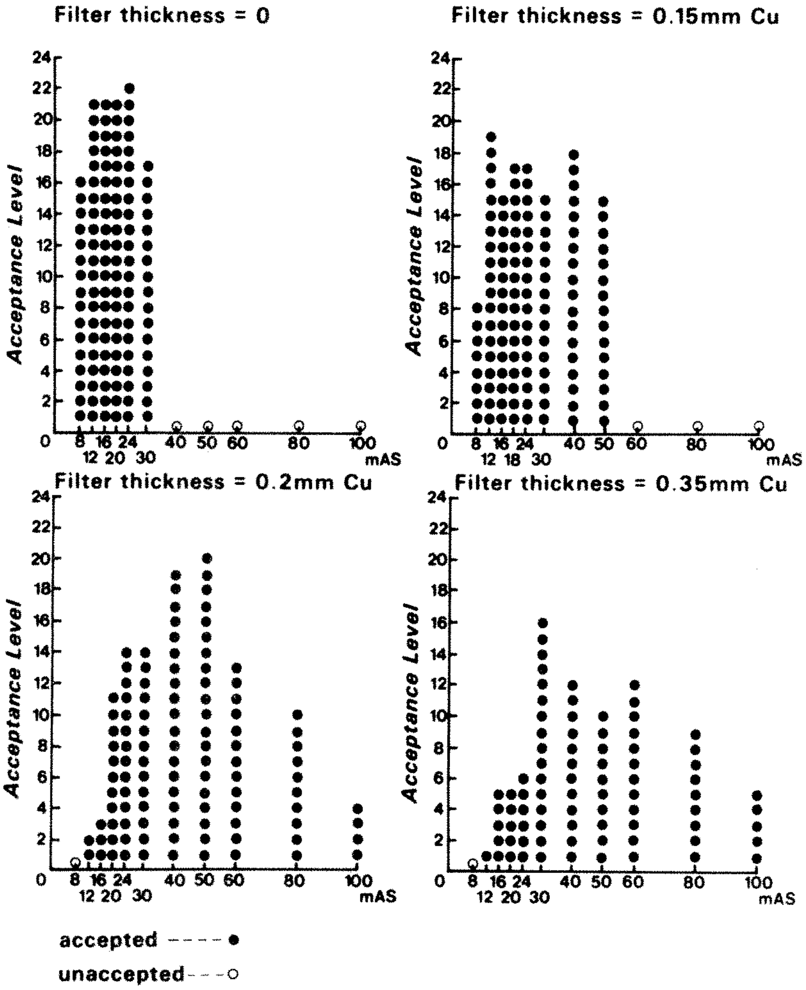
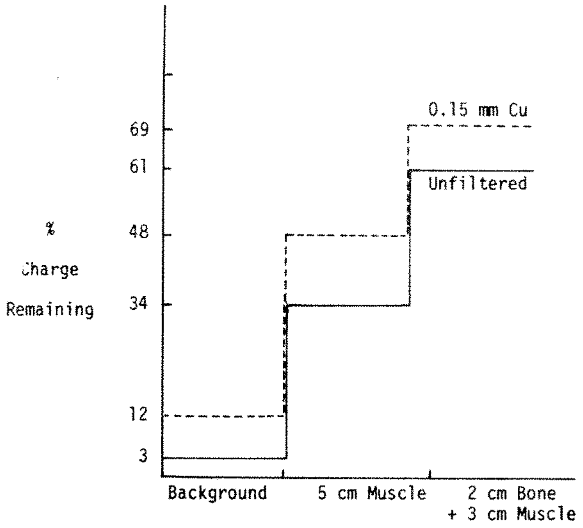


FIG. 6.

The diagnostic "acceptability" of xerograms with added copper filtration. The "acceptance level" is the number of observers who counted a particular xerogram as diagnostic. The total number of acceptances, in order of increasing filter thickness, was 118, 114, 109 and 81.



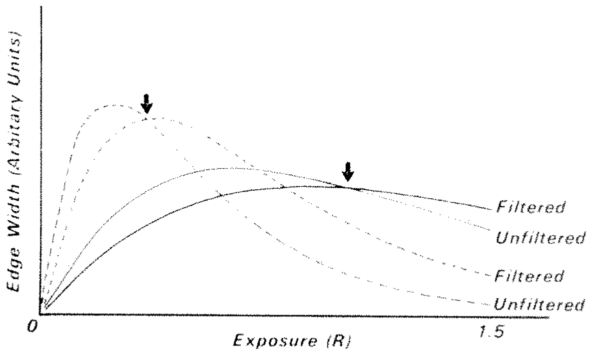


FIG. 8.

The variation of calculated edge width with exposure with practice at other centres, for xerography of the chest and larynx (Davis, 1976; Xerox Corporation, 1973).

The Extent of Dose Reduction

The reduction in exposure achieved by this method has been measured using an ionization chamber. Results show that for X rays generated at 100 kVp, a filter thickness of 0.15 mm reduced the measured exposure to 47% of its original value. From the attenuation coefficient, it is also possible to calculate the reduction in exposure with increasing thickness of filter. Table I shows how the calculated results compare with the measured values. Differences may be attributed to uncertainties regarding the actual inherent filtration present and the effect of scattered radiation on the spectral distribution.

TABLE I

THE EFFECT OF COPPER FILTRATION ON SKIN EXPOSURE*

Filter Thickness (mm)	Exposure as a percentage of that without filtration Calculated	Measured
0	100	100
0.15	52	47
0.2	46	35
0.35	33	26

*These values are for X-rays generated at 100 kVp (single-phase full wave) with a total inherent filtration of 2.7 mm aluminium, at a distance of 100 cm.

PRACTICAL EXPERIENCE

In the past 18 months, over 100 xerograms have been taken in the X-ray department using copper filtration. The majority of these have been produced at a tube voltage of 120 kVp (the maximum available) and with a filter thickness of 0.2 mm copper thereby reducing the exposure of the patient by over 50%. Although a controlled study of the results was not carried out at this stage, the images have been accepted by radiologists and xerograms continue to be requested. It is found, in practice, that in order to achieve optimum quality in these conditions the exposure time has to be increased by about 20% of that used without added filtration (Fig. 9 shows a typical example). However, even taking this into account a reduction in exposure of around 50% is still achieved.

Table II shows that the measured exposures when using xeroradiography with added filtration are much greater than when a screen-film combination is employed but less than for non-screen (high definition) film. It is hoped that future studies of the actual X-ray spectral distribution will make further reduction in dose possible. A controlled comparison of conventional films with xerograms using different thicknesses of filter is currently being undertaken.

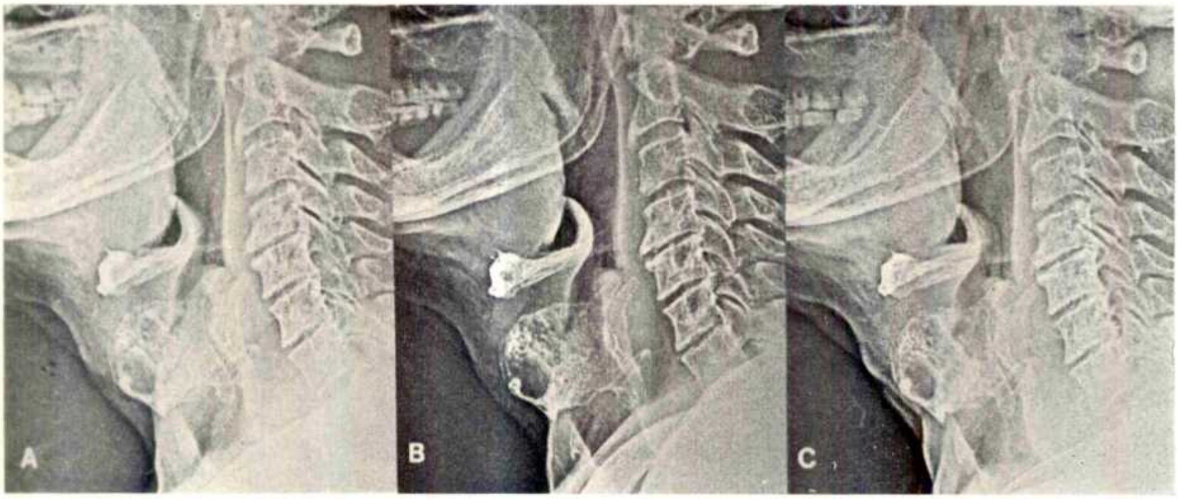


FIG. 9.

Xerogram of lateral neck at 120 kVP (3 phase) and a distance of 120 cm.

(A) 32 mAs; no added filtration.
(B) 40 mAs; 0.15 mm copper.
(C) 40 mAs; 0.2 mm copper.

TABLE II

EXPOSURE FACTORS AND MEASURED EXPOSURES FOR FILM AND XEROGRAM TECHNIQUES*

Part of Body	CEA non-screen film				Screen film				Xerogram without added filtration				Xerogram with 0.2 mm copper			
	kV	mAs	dist. (cm)	exposure (mR)	kV	mAs	dist. (cm)	exposure (mR)	kV	mAs	dist. (cm)	exposure (mR)	kV	mAs	dist. (cm)	exposure (mR)
Hand (PA)	45	40	100	98	40	5	100	8	120	64	100	170	120	8	100	90
Elbow (Lat.)	50	64	100	198	45	5	100	13.5	120	10	100	270	120	13	100	147
Foot (Lat.)	50	64	100	198	45	4	100	11.2	120	10	100	270	120	13	100	147
Knee (AP)	50	160	100	546	50	5	100	17	120	32	100	864	120	40	100	448
Soft Tissue Neck (Lat.)	—	—	—	—	50	32	180	34	120	32	120	600	120	40	120	376

*These exposure factors are for a three-phase generator.

APPENDIX 1

Calculation of the spectrum incident on the plate

Let the unattenuated photon fluence for photons of energy E be P(*E*) photons/cm^2.

Let the thickness of copper filtration added be A cm.

Then the photon fluence for photons of energy E transmitted through the copper is

$$C(E) = P(E) \exp\left\{-\left(\frac{\mu}{\rho}\right)_{\mathrm{Cu}} \rho_{\mathrm{Cu}} A\right\} \text{ photons/cm}^2$$

where ρ Cu = density of copper

$(\mu/\rho)_{\mathrm{Cu}}$ = mass attenuation coefficient for copper

Let the beam pass through a thickness H of muscle and a thickness B of bone before reaching the plate.

Then the photon fluence of photons of energy *E* incident on the plate is

$$D(E) = C(E) \exp\left\{-\left(\frac{\mu}{\rho}\right)_{\mathrm{m}} \rho_{\mathrm{m}} \mathrm{H} - \left(\frac{\mu}{\rho}\right)_{\mathrm{b}} \rho_{\mathrm{b}} \mathrm{B}\right\} \text{ photons/cm}^2$$

where ρ_{m} = density of muscle
ρ_{b} = density of bone
$(\mu/\rho)_{\mathrm{m}}$ = mass attenuation coefficient for muscle
$(\mu/\rho)_{\mathrm{b}}$ = mass attenuation coefficient for bone

The results derived from this calculation must be regarded as approximate as it is not possible to calculate the contribution from scattered radiation, although it is known that secondary radiation exerts less influence in xeroradiography (Selin *et al.*, 1975).

APPENDIX 2

Calculation of the fraction of the original charge remaining on the plate after exposure

As in Appendix 1, let the photon fluence for photons of energy E incident on the plate be *D* (*E*). Then the exposure in Roentgens due to photons of energy *E* (keV) at the position of the plate is:

$$D(E)\, E \left(\frac{\mu\mathrm{en}}{\rho}\right)_{\mathrm{air}} \mathrm{K}$$

where $(\mu\mathrm{en}/\rho)_{\mathrm{air}}$ = mass energy absorption coefficient for air

and $\mathrm{K} = \dfrac{1.6 \times 10^{-9}}{86.9}$ and $(\mu\mathrm{en}/\rho)_{\mathrm{air}}$ K is the conversion factor of energy-fluence to exposure.

From Appendix 1, the total exposure due to all photons for an unattenuated beam is:

$$\sum_{E=0}^{E_{max}} \left(P(E) E \left(\frac{\mu en}{\rho}\right)_{\mathrm{air}} K\right)$$
$$= TK, \text{ say.}$$

Therefore the fraction of this total unattenuated exposure due to photons of energy *E*, after passing through materials such as copper, bone and muscle is:

$$\frac{DE\,(E)\,(\mu en/\rho)_{\mathrm{air}}\,K}{TK} = \frac{D(E)E(\mu en/\rho)_{\mathrm{air}}}{T}$$

If *R* = measured exposure in Roentgens at the plate for an unattenuated beam, then the actual exposure due to photons of energy E that reach the plate is:

$$\frac{DE(E)(\mu en/\rho)_{\mathrm{air}}}{T} R$$

The fraction of charge remaining on the plate, due to photons of energy *E*, is

$$\frac{q}{Q_0} = \exp\{-[0.693\, S(E)\, (\text{exposure due to photons of energy } E)]\}$$

(Boag, 1973)

where q = charge remaining due to exposure to photons of energy *E*
Qo = the initial charge on the plate,

and *S*(*E*) = sensitivity of the plate to photons of energy *E* and is defined as the reciprocal of the exposure required to reduce the charge on the plate to one half.

If Q is the final charge on the plate, then the fraction of charge remaining on the plate due to photons of all energies is:

$$\frac{Q}{Q_0} = \prod_{E=0}^{E_{max}} \left(\frac{q}{Q_0}\right) = \exp\left(-0.693\, \mathcal{J} R/T\right)$$

$$\text{where } \mathcal{J} = \sum_{E=0}^{E_{max}} \left(S(E)\, D(E)\, E\, (\mu en/\rho)_{\mathrm{air}}\right)$$

APPENDIX 3

Calculation of edge width

The width of the edge between two developed areas was investigated by Lewis and Stark (1972) and their results can be represented by the equation

$$\delta = \delta_0 \frac{\triangle V}{V + Vb}$$

where δ_0 = constant
Vb = back bias applied during development
$\triangle V = V' - V$
V' = potential remaining on one side of the edge
V = lower potential remaining on the other side of edge

$$i.e.\ \delta = \delta_0 \frac{V' - V}{V + Vb}$$

$$= \delta_0 \frac{V'/V_0 - V/V_0}{V/V_0 + Vb/V_0}$$

where V_0 = original potential on plate before exposure

but, $\dfrac{V}{V_0} = \dfrac{Q}{Q_0}$ = fraction of charge remaining after exposure

$$\text{therefore, } \delta = \frac{Q'/Q_0 - Q/Q_0}{Q/Q_0 + V_b/Q_0}$$

where Q' = the charge remaining on one side of the edge
Q = lower charge remaining on the other side of the edge
and Q_0 = original charge on the plate

Using the information derived in appendix 2, the edge width δ may be calculated.

REFERENCES

ATKINS, H. L., FAIRCHILD, R. G., ROBERTSON, J. S. and GREENBERG, D., 1975. Effect of absorption edge filtration on diagnostic X-ray spectra. *Radiology*, *115*, 431–437.

BOAG, J. W., 1973. Xeroradiography – review article. *Physics in Medicine and Biology*, *18*, 3–37.

BOAG, J. W., STACEY, A. J. and DAVIS, R., 1976. Radiation exposure to the patient in xeroradiography. *British Journal of Radiology*, 49, 253–261.

DAVIS, R., 1976. Personal communication.

LEWIS, R. B., STARK, H. M., 1972. High sensitivity electrophotographic development: in *Current Problems in electrophotography*. Berg, W. F., Haufe K., eds. New York, De Gruyter, 322–335.

SELIN, K., DEICHGRABER, E., REICHMAN, S., 1975. Influence of secondary radiation on image quality. *Acta Radiologica*, *16*, 520–528.

Xerox Corporation, 1973. Xeroradiography for zonography of larynx and hypopharynx. *Xerox Medical Application Bulletin No. 101.*

Journal review

Environmental International, Vol. 1. Edited by A. A. Moghissi (Pergamon Press, Oxford), $72.60 per annum.

The objective of this new journal as stated in an editorial is to provide a forum for papers on environmental matters for decision makers and scientists. This is a laudable objective but whether it can be achieved will depend on the quality of the papers submitted and accepted by the editor and his editorial board. There are of course many other journals in this field, such as *Environmental Research*, *Environmental Policy and Law*, and *Atmospheric Environment*, and the decision-maker, that ubiquitous shadowy figure, may prefer to read one or all of these.

The first edition of *Environment International* is filled by papers from a symposium "Metrology needs in the measurement of environmental radioactivity", held in Paris in October 1976. These are highly specialized papers from a meeting held over 18 months ago which might well have been more appropriately published in a journal of radiochemistry, for many of them deal with the problems of detecting and measuring radioactivity at low levels. In fact for a reader interested in the broad spectrum of science and technology applied to environmental problems, this first issue is unattractive. It might have been better had the editor invited a few well known scientists working in the environmental field to contribute review articles on the major environmental problems facing modern developed communities.

It is clear that the reviewer was not impressed by the first number of the journal, possibly owing to a high expectation after reading the editorial. A potential subscriber to this journal would be well advised to appraise two or three more copies before deciding on whether to spend about £40 per year.

G. W. DOLPHIN.

1978, *British Journal of Radiology*, *51*, 981–985 DECEMBER 1978

Limitations of the single sample tracer method for determining glomerular filtration rate

By B. E. Chatterton, M.B., B.S., F.R.A.C.P.

Division of Nuclear Medicine, Institute of Medical and Veterinary Science, Adelaide, South Australia 5000

(*Received November, 1977 and in revised form January, 1978*)

ABSTRACT

Apparent volumes of distribution of ^{51}Cr-EDTA and ^{99}Tc^{m}-DTPA were calculated three hours after intravenous injection and correlated with simultaneous estimation of GFR. A reasonable correlation between these values was obtained for those patients with GFR > 50 ml/min (standard error of estimate using ^{51}Cr-EDTA 7.6 ml/min and ^{99}Tc^{m}-DTPA 13.7 ml/min). Theoretical reasons are given why a single sample technique will not be accurate over a wide range of renal function.

An accurate but simple measurement of glomerular filtration rate (GFR) in routine clinical practice has long been required. Due to variability in endogenous production, the correlation of serum creatinine or blood urea nitrogen with glomerular filtration rate is not high. The measurement of creatinine clearance is more accurate, but involves timed urine samples and, even when performed reliably, does not correlate well with inulin clearance, the accepted standard method of estimating GFR (Dodge *et al.*, 1967). This paper explores the theory and performance of one of the simplest methods of estimating GFR, a single injection–single sample technique, and demonstrates its limitations.

THEORY

Classically, GFR has been measured by an iv infusion of inulin until a steady plasma concentration is reached. This is a time-consuming and relatively invasive method, with the additional problem that the chemical estimation of inulin is difficult. Certain radioactive tracers, such as ^{51}Cr-EDTA, have been shown to be cleared at a rate very similar to inulin, and are more easily assayed (Garnett *et al.*, 1967). They have therefore become a popular substitute. More recently, techniques involving a single injection and measurement of the disappearance from plasma have obviated the need for an iv infusion, a high correlation having been shown between these methods (Chantler *et al.*, 1969).

The typical plasma time–activity curve for a patient given a single iv dose of tracer cleared by glomerular filtration may be resolved into two exponential components, one fast and one slow. Hence the curve may be described by the formula:

$$C_t = Ae^{-b_1 t} + Be^{-b_2 t} \quad . \quad . \quad . \quad (1)$$

where C_t is the concentration at time t, and A and b_1, B and b_2 are the intercepts and slopes of the fast and slow components respectively.

Sapirstein *et al.* (1955) have shown that a two-compartment mammillary system is a valid model for this physiological phenomenon, and quote formulae by which the following parameters may be calculated using the disappearance curve: V_1, the volume of the compartment injected and sampled which includes the plasma; V_2, the volume of a rapidly exchanging compartment (the sum of $V_1 + V_2$ approximates to the extracellular fluid); the rate constants, K_{12} and K_{21} representing the rate of diffusion from V_1 to V_2 and vice versa, and K_{13} representing the one-way removal from the plasma by glomerular filtration (GFR $= V_1 K_{13}$).

To define the disappearance curve accurately, multiple blood samples or continuous external monitoring are needed, necessitating prolonged attention to the patient; because of this, several authors have described methods of reducing the number of blood samples needed. Fisher and Veall (1975) published empirical relationships of timed single-sample concentrations with GFR, following the lead of Tauxe *et al.* (1971) who pioneered a similar method for the estimation of effective renal plasma flow (ERPF). An empirical approach has several disadvantages. For example, the function that Tauxe chose to represent the relationship between plasma concentration and ERPF was a quadratic with a maximum value of 554 ml/min. This value of renal plasma flow is exceeded by more than 50% of normal adults (Smith *et al.*, 1938). Correction for the size of the patient may also be approached more easily from theory than on an empirical basis. A convention for the measurement of plasma concentration of tracer was established by Tauxe and this was followed by Fisher. They chose their measurement of plasma concentration to indicate the apparent volume of distribution at a time t after injection of dose I, I/C_t, defined by:

$$\frac{I}{C_t} = \frac{\text{activity injected}}{\text{plasma concentration at time } t} \text{ litres} \quad . \quad (2)$$

According to Matthews (1957), the proportion of injected tracer X_1 in V_1 at time t is given by:

$$X_1 = \frac{K_{21}-b_1}{b_2-b_1} e^{-b_1 t} + \frac{K_{21}-b_2}{b_1-b_2} e^{-b_2 t} \quad . \quad . \quad . \quad (3)$$

where $b_1 + b_2 = K_{21} + K_{12} + K_{13}$

and $\quad b_1 b_2 \quad = K_{21}\, K_{13}$

$$\text{Hence } \frac{I}{C_t} = \frac{V_1}{X_1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where X_1 is given by equation (3).

Knowing the above parameters in a given patient, one may calculate expected values of I/C_t for a range of GFR.

If $K_{12} >> K_{13}$, then little error should be introduced by assuming that V_1 and V_2 are combined as a single compartment. If this is assumed, it can be shown that, for such a system,

$$\frac{I}{C_t} = (V_1 + V_2)\, e^{\left[\frac{\text{GFR}}{V_1+V_2}\right] t} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

(for derivation see Appendix 1).

Fisher and Veall (1975) suggested that correction for the body surface area of the patient may improve the accuracy of the sample method, but offered no suggestion as to how this could be done. In effect, the single sample method uses many points to define a curve, with an assumed relationship of the other points to the sample taken. Obviously this assumption implies a constant value for the size of compartments V_1 and V_2, and rate constants K_{12} and K_{21}.

If some relationship exists between these values and the size of the patient, it might be possible, with difficulty, to correct equation (4) for these variables. To correct equation (5) is a much simpler task and may be done by the following formula if one assumes that $(V_1 + V_2)$ has a relationship with patient size, *viz.*

$$\frac{I}{C_t}(c) = y \left[\frac{\frac{I}{C_t}(p)}{x} \right]^{\frac{x}{y}} \quad . \quad . \quad . \quad . \quad (6)$$

(for derivation see Appendix 2).

Method

Following a single intravenous injection of 100 μCi of ^{51}Cr-EDTA (Australian Atomic Energy Commission, Lucas Heights, New South Wales,

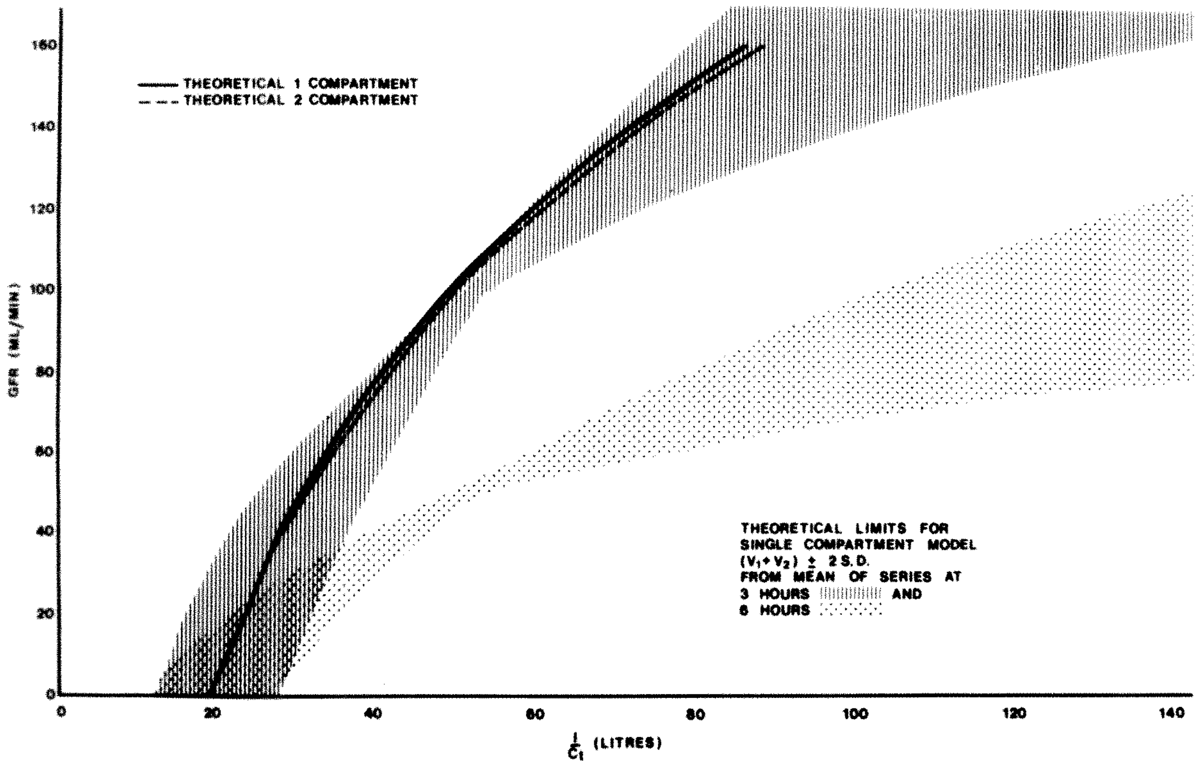


Fig. 1.

Theoretical values of I/C_t for one and two compartment models and theoretical confidence limits at three and six hours $(V_1 + V_2) \pm 2$ S.D. (see text).

Australia), the plasma disappearance curve was monitored for three hours by multiple blood samples in 31 patients. The curve was resolved into two exponential components by graphical curve "stripping" and V_1, V_2, K_{12}, K_{21} and GFR calculated as described. The apparent volume of distribution of ^{51}Cr-EDTA (I/C_t) was calculated at three hours, and I/C_t was also calculated three hours following the iv injection of ^{99}Tc^m-DTPA (Australian Atomic Energy Commission) within 24 hours of the ^{51}Cr-EDTA GFR estimation.

RESULTS

The mean values for V_1, V_2, K_{12}, and K_{21} were 10.9 l, 8.4 l, 0.110 min^{-1}, and 0.085 min^{-1}, respectively. The mean value of K_{13} was 0.0054 min^{-1} and hence of GFR was 59 ml min^{-1}.

Applying these values to equations (3) and (4), the theoretical curve in Fig. 1 was obtained which represents the apparent volume of distribution at three hours in a "standard" patient with parameters equal to the mean of this series for a range of GFR from 0–160 ml/min using a two-compartment model. As $K_{12} > K_{13}$, equation (5) was rearranged and used to plot a similar curve assuming a single compartment model. The resulting equation was GFR (ml/min) $= -317 + 107 \ln (I/C_t)$. As can be seen (Fig. 1) very little error is introduced by this assumption.

An attempt was then made to correlate V_1 and V_2 and associated rate constants with the size of the patient. Although there is a weak correlation between these parameters and the height, weight, and body surface area of the patient, the strongest correlation was between $(V_1 + V_2)$ and the patient's weight, such that

$(V_1 + V_2)$ litres $= 9.45 + 0.159$ wt (kg) ($r = 0.48$)

However, the standard error of the estimate of this function was 3.93 litres with similar variability both in patients with renal failure and those with normal function.

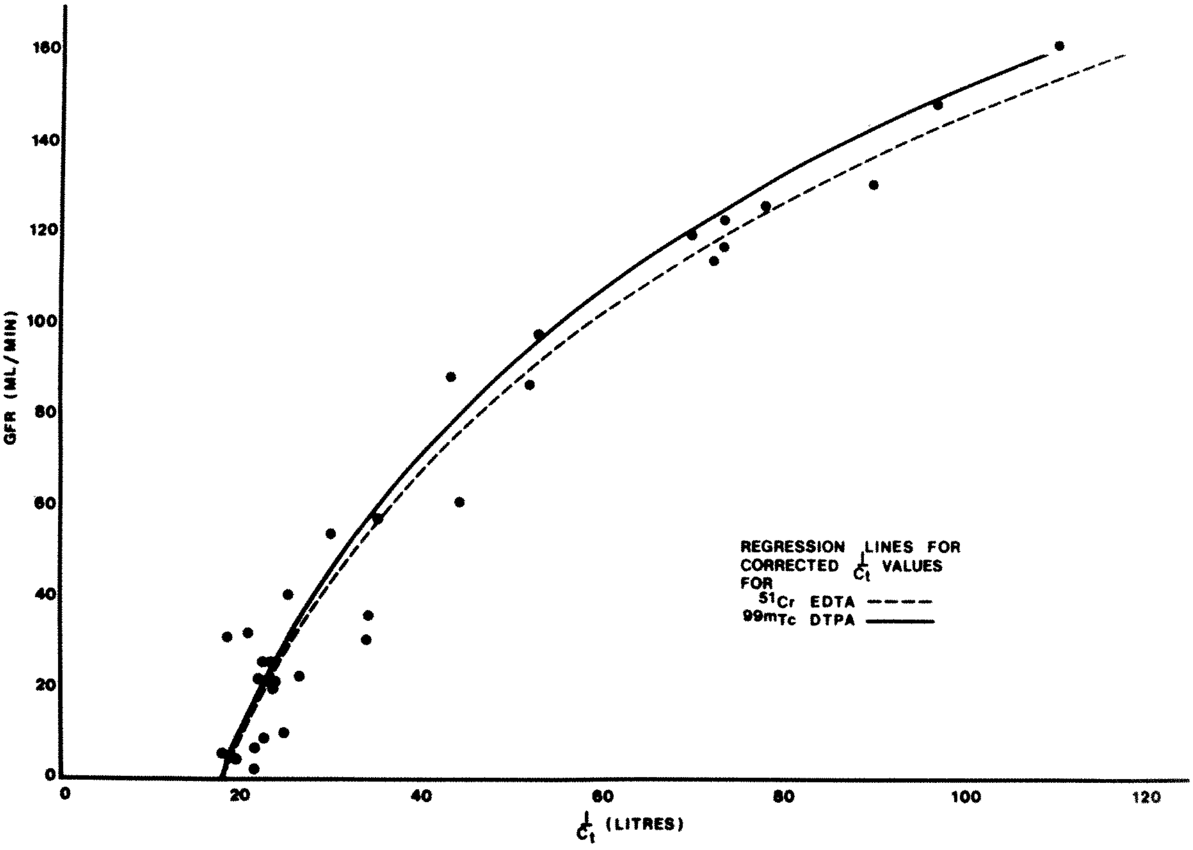


FIG. 2.

The apparent volume of distribution I/C_t for ^{51}Cr-EDTA (corrected for patient weight) plotted *v.* GFR, with associated regression line. Also shown is regression line for corrected values of ^{99}Tc^m-DTPA.

Also plotted on Fig. 1 are the limits of estimates using a single compartment model of I/C_t for patients with estimated $(V_1+V_2)\pm 2$ S.D. from the mean of our series, with sampling times at three and six hours.

The apparent volumes of distribution of ^{51}Cr-EDTA at three hours, standardized for bodyweight, are plotted in Fig. 2, with the corresponding least square regression line $\mathrm{GFR}=-246+85.2 \ln (I/C_t)$. The standard error of the estimate over all values is 10.9 ml/min, but for GFR greater than 50 ml/min it is 7.6 ml/min. The correction of I/C_t for body weight decreases the standard error of the estimate by only 1.0 ml/min, which is not statistically significant.

The regression line for standardized I/C_t for ^{99}Tc^{m}-DTPA is also shown in Fig. 2: $\mathrm{GFR}=-255+88.8 \ln (I/C_t)$. The standard error of the estimate was 13.8 ml/min, with no significant difference between high and low values of GFR. Again, correction for bodyweight failed to improve this error significantly.

DISCUSSION

Because of the steepness of the curve and the wide confidence limits for estimates of low GFR, measurements of I/C_t do not give a useful estimate below a GFR of about 50 ml/min.

Although not tested in practice, it appears theoretically that a sample taken at six hours would give improved accuracy at low levels, but reduced accuracy at normal renal function (Fig. 1). However, no single routine time of sampling gives a sufficiently accurate estimate over the range encountered clinically, and multiple samples negate the attractiveness of the technique.

The slightly greater variability of the results obtained with ^{99}Tc^{m}-DTPA is possibly due to increased and more variable protein binding compared with ^{51}Cr-EDTA (Klopper *et al.*, 1972).

CONCLUSION

Although a reasonably accurate estimate of GFR may be obtained over a moderate range of renal function using a single timed sample of blood following an iv injection of ^{51}Cr-EDTA or ^{99}Tc^{m}-DTPA, no single time can give a sufficiently reliable result over the entire range encountered clinically. Correction factors based on estimates of the extracellular volume using the size of the patient are too inaccurate to improve the result to a significant extent, and in practice, unless more accurate methods of predicting this volume are found, the more complex methods of estimating GFR involving multiple samples are necessary.

APPENDIX 1

Assuming a single compartment model,
$\mathrm{GFR}=k\,(V_1+V_2)$.
Let plasma concentration at time $t=C_t$.
Let activity injected $=I$

Theoretical volume of distribution at time $t=\dfrac{I}{C_t}$

Theoretical volume of distribution at time 0

$$=\frac{I}{C_0}=(V_1+V_2)$$

For exponential clearance $C_t=C_0e^{-kt}$

$$\text{or } \frac{C_t}{I}=\frac{C_0}{I}\,e^{-kt}$$

Therefore

$$\frac{I}{C_t}=\frac{I}{C_0}\,e^{kt}$$

Therefore

$$\frac{I}{C_t}=(V_1+V_2)\,e^{\left[\frac{\mathrm{GFR}}{V_1+V_2}\right]t} \quad \text{which is equation} \quad (5)$$

$$\text{Also } \ln\frac{I}{C_t}=\ln (V_1+V_2)+\frac{\mathrm{GFR}}{(V_1+V_2)}\,t$$

Therefore

$$\mathrm{GFR}=\frac{(V_1+V_2)}{t}\left(\ln\frac{I}{C_t}-\ln (V_1+V_2)\right)$$

APPENDIX 2

Let x=predicted (V_1+V_2) in patient
y=predicted (V_1+V_2) in "standard" patient

$\dfrac{I}{C_t}(p)$=volume of distribution in patient

$\dfrac{I}{C_t}(c)$=volume of distribution, corrected for patient size.

For constant GFR:

$$x\,\frac{\left(\ln\dfrac{I}{C_t}(p)-\ln x\right)}{t}=y\,\frac{\left(\ln\dfrac{I}{C_t}(c)-\ln y\right)}{t}$$

(from last equation of Appendix 1).

$$\text{hence } \frac{I}{C_t}(c)=y\left[\frac{\dfrac{I}{C_t}(p)}{\mathrm{x}}\right]^{\frac{\mathrm{x}}{\mathrm{y}}} \quad \ldots\ldots \quad (6)$$

REFERENCES

CHANTLER, C., GARNETT, E. S., PARSONS, V., and VEALL, N., 1969. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr-EDTA. *Clinical Science, 37*, 169–180.

DODGE, W. F., TRAVIS, L. B., and DAESCHNER, W. C., 1967. Comparison of endogenous creatinine clearance with inulin clearance. *American Journal of Diseases in Childhood, 113*, 683–692.

FISHER, M., and VEALL, N., 1975. Glomerular filtration rate based on a single blood sample. *British Medical Journal, 2*, 542.

GARNETT, E. S., PARSONS, V., and VEALL, N., 1967. Measurement of glomerular filtration rate in man using a ^{51}Cr/Edetic-acid complex. *Lancet, 1*, 818–819.

KLOPPER, J. F., HAUSER, W., ATKINS, H. L., ECKELMAN, W. C., and RICHARDS, P., 1972. Evaluation of ^{99}Tc-^{m} DTPA for the measurement of glomerular filtration rate. *Journal of Nuclear Medicine, 13*, 107–110.

MATTHEWS, C. M. E., 1957. The theory of tracer experiments with ^{131}I labelled plasma proteins. *Physics in Medicine and Biology, 2*, 36–53.

SAPIRSTEIN, L. A., VIDT, D. G., MANDEL, M. J., and HANUSEK, G., 1955. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *American Journal of Physiology, 181*, 330–336.

SMITH, H. W., GOLDRING, W., and CHASIS, H., 1938. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *Journal of Clinical Investigation, 17*, 263–278.

TAUXE, W. N., MAHER, F. T., and TAYLOR, W. F., 1971. Effective renal plasma flow. Estimation from theoretical volumes of distribution of intravenously injected ^{131}I orthoiodohippurate. *Mayo Clinic Proceedings, 46*, 524–531.

Book review

Encyclopaedia of Urology V/1 Supplement, Diagnostic Radiology. By L. Andersson, I. Fernström, G. R. Leopold, J. U. Schlegel and L. B. Talner. pp.ix + 199, illus. (Springer-Verlag KG, New York, Berlin, London), $60.00, DM98.00.

This slim volume is presented as a supplement to the corresponding volume in the Encyclopaedia of Urology published in 1962. It comprises three separate and distinct sections; the first is headed Radionuclides in Urology and occupies 65 pages with a further 16 pages of references; the second is headed Urological Ultrasonography and occupies 43 pages with two-and-a-half pages of references; the third is entitled Percutaneous Puncture Nephrostomy and is 46 pages long with less than half a page of references.

The first section is predominantly concerned with the use of ^{131}I Hippuran utilizing a gamma scintillation camera which the author has used with an essentially unchanged technique for ten years. Other techniques are included but the discussions on these are relatively brief. Overall the use of radionuclides in urology is well argued with clear indications of their advantages and limitations. This section abounds with practical information on the conduct of the investigation and includes full discussion of the theoretical considerations governing interpretations. The illustrations are of high quality and the diagrams have been well drawn with great clarity. There is a very full list of useful references up to 1974.

The second section is effectively much shorter as this is largely occupied by excellent illustrations both of the ultrasonagrams and of the corresponding urograms and angiograms. It is a very readable review of the place of ultrasonography but of necessity presents a rather superficial discussion of the subject. The references are well selected but are relatively sparse.

The third section is a very full review of the useful technique of needle nephrostomy, supported by numerous case reports. The method is presented with enthusiasm and conviction and contains a full description of both the practical considerations and possible complications. Whether this technique deserves space approximately equalling that given to radionuclides and to ultrasonography is open to question.

The first paragraph of the preface contains the astonishing claim that despite the passage of some sixteen years the original volume on diagnostic radiology is still essentially valid. It is tempting to suggest that this view may be in part explained by the inclusion in separate parts of the first section of the statements that 18–20 grams or more of diatrizoate or iodothalamate may be used for excretion urography; 50% of routinely performed intravenous urograms for screening procedures are basically non-diagnostic; and that intravenous urography in the azotaemic patient is often little or no help except in acute obstruction. While the supplement is an excellent concise review of the development of three techniques important in the study of uroradiology, in no way can it be held to update successfully the original publication. This supplement is well worth reading, can be recommended to any interested in the practice or teaching of uroradiology, but should be used in conjunction with a modern standard textbook on the subject.

JOHN ROYLANCE.

1978, *British Journal of Radiology*, *51*, 986–991

The influence of size and radiopharmaceutical concentration ratio on the detection of abnormalities in clinical radionuclide imaging

By A. V. Lakshmanan* B.Sc., Ph.D.,

Department of Medical Physics, Cancer Institute, Madras 600020, India

P. Sharp, B.Sc., Ph.D. and J. Mallard, Ph.D., D.Sc., F.Inst.P.

Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen, Aberdeen

(*Received July, 1977 and in revised form January, 1978*)

ABSTRACT

The effect of the size of an abnormality on its detectability was measured. The cylindrical abnormalities studied, with diameters ranging from 3 mm to 4 cm, were superimposed on a uniform background.

To avoid artefacts produced by the imaging devices, the images were simulated by computer. The method of constant stimulus was used to determine the detectability of the abnormalities.

By using a Perspex phantom filled with ^{99}Tc^{m}, measurements were made of the concentration ratio between abnormality and background which permitted detection of the abnormality. This allowed evaluation of the effectiveness of ^{99}Tc^{m} pertechnetate in the detection of small abnormalities.

Assuming a concentration ratio between abnormal and normal tissue of 22.5:1, then at a depth of 50 mm in the brain a cylindrical abnormality of about 8 mm diameter was the smallest detectable under the chosen scanning conditions.

Whether or not a lesion will be visible on a scan depends upon a number of parameters including collimator resolution and sensitivity, the concentration of radiopharmaceutical in the lesion, the size and location of the lesion and how effectively the final image is displayed. Dewey and Sinclair (1961), Beck (1961) and Matthews (1964) first derived mathematical relationships to describe the contrast on the scan image between the lesion and the surrounding tissue as a function of some of these parameters. They proposed a statistical test to decide whether the contrast is sufficiently great to permit detection of the lesion. However, these theories may not accurately predict what can be seen on real displays (Mallard and Wilks 1968).

Matthews (1964) described an experiment in which observers were shown count-rate profiles of scans of a background tank of radionuclide containing a Perspex sphere filled with radionuclide to represent the lesion. She deduced that the results of viewing these profiles supported the statistical theories of detection, but few details were given.

Elaborations of the basic statistical theory as applied to radionuclide imaging have been proposed by Mallard and Corfield (1969), Sharma and Fowler (1970) and Sharp and Mallard (1974) but none have been sufficiently developed to permit the prediction of an observer's visual response to an image. Also, there is a lack of experimental measurements to determine what an observer can see in the images.

Telander and Loken (1967) made measurements using a head phantom containing spherical abnormalities of various sizes. Images produced with a rectilinear scanner and a gamma camera were viewed by observers and an estimate made of the effect of the size of the abnormality on its detectibility. A similar experiment was performed by Mallard and Wilks (1968), using a rectangular tank.

It is difficult in such experiments to ensure that the perceptibility of the abnormality is not mainly influenced by factors peculiar to the particular imaging device used, these representing uncontrolled and ill-defined variables in experiments designed primarily to measure the influence of other parameters. This problem was overcome by Schulz *et al.* (1970), who simulated the image of a kidney containing a "cold" lesion. However the value of their results was limited because they only dealt with completely "cold" lesions.

A further problem is that of measuring how well a lesion is seen in an image. This has been investigated by using a computer simulation of the image of a uniform background distribution on which was superimposed the image of a cylindrical abnormality (Sharp and Mallard, 1976, 1977, Sharp 1976). The image contrast, IC, between the abnormality and background is defined by

$$\mathrm{IC}=\frac{D_A-D_B}{D_B}$$

where D_A is the maximum count density in the image of the abnormality and D_B is the mean background count density. In the quoted studies D_B was kept constant and a set of images was produced containing a range of values of D_A. For each value of

D_A several images were made and the observer's visual response, *i.e.* percentage of images in which he correctly identified the abnormality, was plotted against D_A. The value of D_A which produced a 50% visual response from the observer was taken as that at which the observer would detect the abnormality. The corresponding value of IC was called the detection contrast. This method of measuring visual performance is known as the method of constant stimulus and is a standard psychometric procedure (Corso, 1967).

Thus a combination of computer simulation of the images with the method of constant stimulus allows a precise quantitative definition of what count densities the abnormality and background must have if the abnormality is to be detected. We have used these techniques to determine the effect on the detectability of a cylindrical abnormality of changing its diameter and the concentration ratio between abnormality and background. The concentration ratio, CR, is here defined by the relationship:

$$CR = 1 + \frac{C_A}{C_B}$$

where C_A is the concentration of radionuclide in the abnormality, as measured in units of activity per unit volume, and C_B is that in the background. The results obtained have been used to predict the smallest abnormality detectable in brain imaging with $^{99}Tc^m$ pertechnetate.

EXPERIMENTAL METHOD

In order to represent approximately the conditions found in brain scanning, a background tank of dimensions 250 × 150 × 100 mm was used, but measurements were also made with a tank of 300 × 210 mm cross-sectional dimensions, and for different depths of liquid, to see how critical was the choice of dimensions of the phantom. The abnormalities consisted of a set of five hollow cylinders, 10 mm in height, with a wall thickness of 1 mm and internal diameters of 3, 5, 10, 20 and 40 mm. Their profile shapes were measured on three imaging devices; a Nuclear Enterprises Mark V γ-camera, an Elscint Whole Body Scanner, and the Aberdeen Section Scanner (ASS) (Bowley *et al.*, 1973) used in its conventional rectilinear scan mode. Details of collimation and pulse-height analyser settings are given in Table I.

In order to measure the relationship between the contrast in the image, IC, and the concentration ratio, CR, the abnormalities and the background tank were filled with known concentrations of the radionuclide, determined with an isotope assay calibrator (Model 238, Pitmans Ltd., Surrey, England). Instead of suspending the abnormality in a tank of radioactive liquid, the count-rates from the abnormality and the background were measured separately (Mallard and Wilks, 1968). One set of measurements of count rate from the abnormality was made in air, representing the count rate expected from a superficial lesion, and a second set with 50 mm of Mix D tissue-equivalent material between the abnormality and the collimator to simulate a deep lesion. All measurements were made at the collimator focus for the two scanners and either on the collimator face of the γ-camera or 50 mm away when the Mix D was present.

These measurements were then used in the computer simulation of the test pattern. The program, described in Lakshmanan (1975), allows the operator to vary the profile shape, profile size, image contrast and background count density.

The final images were displayed on a Nuclear Data 50:50 system, the display containing 64 × 64 elements, each element representing an area of 4 mm square. Grey shades were allocated to the image count densities according to the statistical level

TABLE I

DETAILS OF COLLIMATORS AND PULSE HEIGHT ANALYSER SETTINGS

Instrument	Focal length mm	Full width at half maximum height mm	Energy settings keV
Elscint Whole Body Scanner with VC4 collimator	90	15	130–170 (automatic setting)
Aberdeen Section Scanner with "depth independent" collimator (see Lakshmanan *et al.*, 1975)	160	10	120–170
Nuclear Enterprises Mk V γ-camera	FWHM measured at 50 mm from collimator face	13	129–151 (automatic setting)

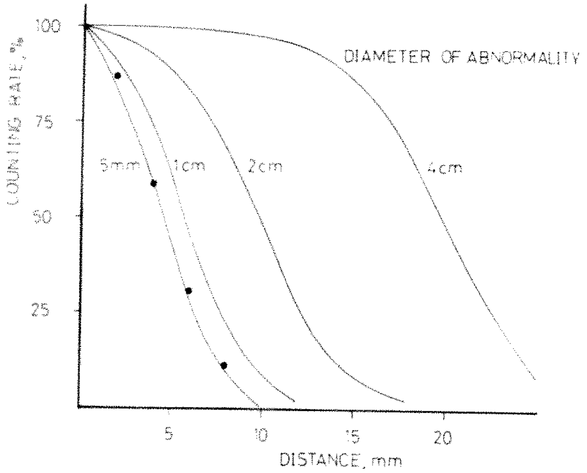


FIG. 1.

The count-rate profiles along the diameters of the 5 cylindrical abnormalities, as measured in air on the ASS. The experimental points are shown only for the 3 mm abnormality and are denoted by filled circles (•).

system, using optimum band widths as defined by Sharp and Mallard (1976).

Pictures of the displayed images were taken on Polaroid type 107C film and the method of constant stimulus used to measure the observers' visual response as a function of image contrast. The detectability of a particular size of abnormality, for a given background count density, was defined by the detection contrast, which is the image contrast which produces a 50% true positive visual response from the average observer.

RESULTS

Figure 1 shows how the shape of the count-rate profile changed as the size of the abnormality was varied. The profiles for the 3 mm and 5 mm diameter abnormalities were identical. These measurements were made on the ASS with no scattering material present. Similar profile values were then used in the computer simulation.

The effect of profile shape and size on the detectability of the abnormality is shown in Fig. 2. These results are for abnormalities with the profiles of Fig. 1. Image size is defined as the full width at half maximum height (FWHM) of the image profile and all measurements are at the same background count density of 80 counts per display element (cpe). There is a non-linear relationship between abnormality size and the contrast needed for detection.

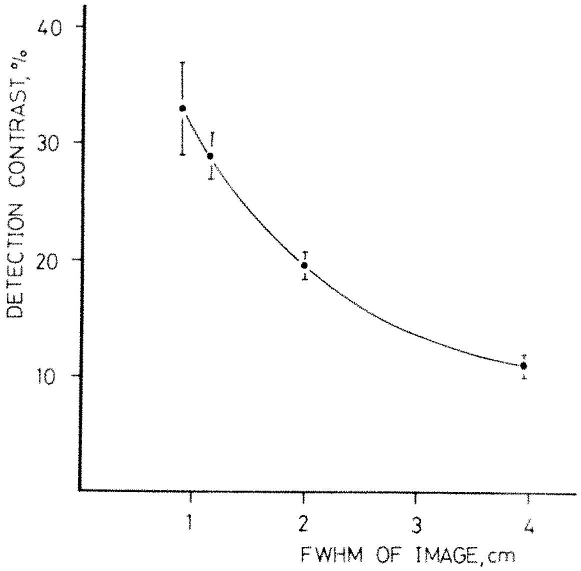


FIG. 2.

Effect of the size of the image of the abnormality, as measured by its full width at half maximum height, on the detection contrast. The profile shapes of the abnormalities are those shown in Fig. 1 and the background count density is 80 counts per display element (cpe). The curve fitting was performed by eye.

The influence of background count density on the detection contrast is demonstrated in Fig. 3. These measurements are of images containing an abnormality of 20 mm FWHM.

The variation of image contrast, IC, with concentration ratio, CR, was, as expected, linear for all imaging devices and sizes of abnormality.

Increasing the cross-sectional dimension of the background tank to 300×210 mm had no effect on the count-rate recorded by the scanners, but increasing the tank depth to 150 mm while keeping the total activity constant, did lead to a drop in the count-rate owing to attenuation of the gamma rays.

DISCUSSION

As would be expected, large abnormalities were detected at a lower contrast than small abnormalities; an abnormality whose image had a FWHM of nearly 40 mm was detected when its maximum count density was only 1.11 times higher than the background count density of 80 cpe, whereas a contrast of 33% was needed to detect the 9 mm FWHM abnormality.

Detection contrast depends not only on abnormality size but also on background count density. Figure 3 shows how increasing the background count density makes it easier to detect the abnormality. This approximately inverse square root relationship between detection contrast and background count density can be predicted (Sharp and

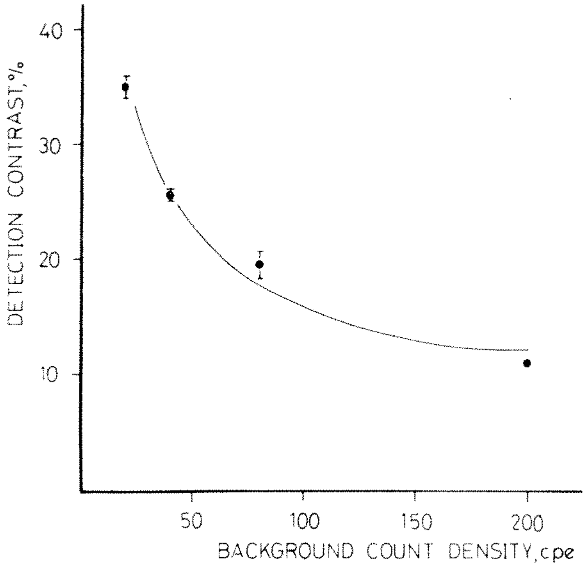


FIG. 3.

The variation of detection contrast with background count density, the image of the abnormality having FWHM of 20 mm, and a profile shape as shown in Fig. 1. The curve is that predicted by the method of Sharp and Mallard (1976) using the value of detection contrast as measured at the background count density of 40 cpe.

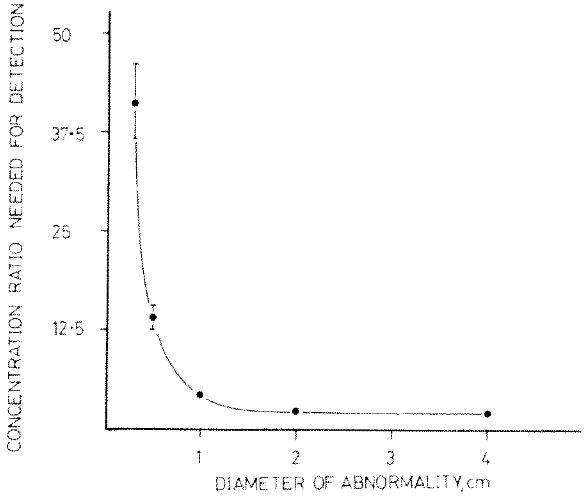


FIG. 4.

The concentration ratio needed in order to detect an abnormality of a partiular size using the ASS. The background count density was 80 cpe, the depth of liquid in the background tank was 100 mm and there was no scattering medium between the abnormality and the detector. The curve was fitted by eye.

Mallard, 1976). There is good agreement between the predicted curve and the experimental results.

These results are quite general and apply to any imaging device which produces the same shape of count-rate profile from the abnormality and which uses a statistical display system. Detectability is measured in terms of imaged count density, but by using the measurements taken from the phantom they can be expressed in terms of the distribution of the radionuclide. The resulting values are then also dependent upon the actual imaging device used. Thus the measurements made with the phantom relate the size of the image, as measured by its FWHM, to the diameter of the abnormality, and relate the image contrast to the concentration ratio.

In Fig. 4, the concentration ratio between abnormality and background needed to produce an image in which the abnormality can be detected is plotted as a function of the diameter of the abnormality. This figure shows the results of Fig. 2 expressed in terms of the actual physical distribution of radionuclide. It can be seen how rapidly the concentration ratio must increase if small abnormalities, *i.e.* less than 10 mm in diameter, are to be detected in the image. This rapid rise in the curve is a result of the fact that abnormalities whose physical size is smaller than the FWHM of the collimator have approximately the same size on the final image. The count-rate profiles of the 3 and 5 mm abnormalities are identical, as can be seen in Fig. 1, and so they will have the same detection contrast, but since the volume of the 3 mm abnormality is less than that of the 5 mm one it will require a higher concentration of radionuclide to produce the same contrast in the image. For abnormalities whose size exceeds the system resolution, size has little effect on the concentration ratio needed for detection.

As with the detection contrast, the concentration ratio needed for detection decreases with increasing background count density (see Fig. 5). Since concentration ratio and image contrast are linearly related, the concentration ratio needed for detection varies with the inverse square root of background count density as did the detection contrast. Therefore, although the concentration ratio needed for detection can be significantly reduced by avoiding low count densities, by, for example, increasing the scan time or increasing the amount of radiopharmaceutical administered to the patient, the benefit becomes less with increasing count density in the background.

In clinical practice the concentration ratio is determined by the radiopharmaceutical used and, to some extent, by the type of lesion present. The dimensions of the background tank were chosen to represent those of the human head and so it is of interest to consider what the above results imply about the performance of the commonly used ^{99}Tc^{m}-pertechnetate brain-scanning agent. Measurements made on animals with transplanted brain tumours have shown concentration ratios between 15:1 and 30:1 (McAfee and Subramanian, 1975). An average value of 22.5:1 is used here.

Table II shows the smallest size of abnormality which can be detected at the concentration ratio of 22.5:1 using the three imaging devices, the background count densities being those recorded over the cerebral hemispheres in routine brain-scanning in Aberdeen. The smallest detectable abnormality has a diameter of 5 mm if situated superficially and about 8 mm if 50 mm deep in tissue. This minimum detectable size changes only slowly with count density when the size of the abnormality is less than 10 mm. To detect a 3 mm diameter lesion, 50 mm deep in Mix D, background count densities of 2940, 1108 and 728 cpe are required on the Elscint Scanner, ASS and γ-camera respectively. However, to detect a 10 mm lesion under the same conditions, the corresponding background count densities are 32, 7 and 8 cpe. Therefore it appears that this radiopharmaceutical concentrates sufficiently well for lesions 10 mm in diameter to be detected.

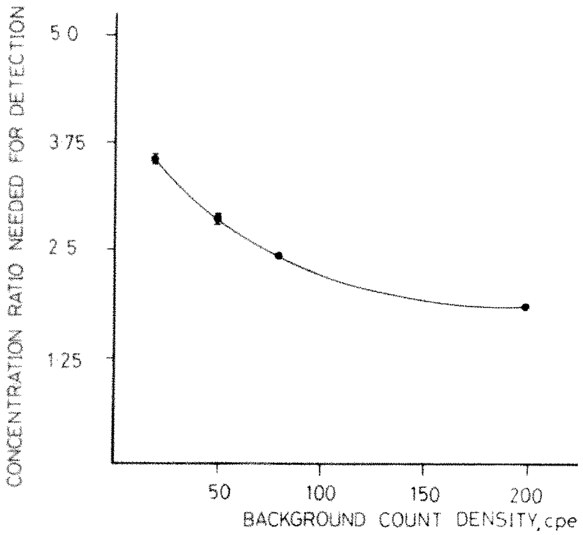


FIG. 5.

The effect of background count density on the concentration ratio needed to detect the 20 mm diameter abnormality using the ASS. The curve was fitted by eye.

For the 3 mm lesion to be detected in 50 mm of Mix D at these brain scan count densities the required concentration ratio would need to be 131, 81 and 93 for the Elscint, ASS and γ-camera respectively.

The applicability of these results to clinical brain scanning is, of course, dependent upon the model of the uniform distribution of radionuclide chosen to represent the brain although variation in the size of the background tank had little effect on the size of the detectable abnormality as can be seen in Table II.

Telander and Loken (1967) found that the smallest detectable spherical abnormality had a volume of 0.9 cm^3 when situated superficially and 1.45 cm^3 when placed at the mid-line of their phantom. These measurements were made on a γ camera at a background count density of 125 cpe and a concentration ratio of 15:1. Under the same conditions our measurements indicate that in the superficial position a 4 mm cylindrical abnormality should be detectable, *i.e.* a volume of 0.12 cm^3, while close to the mid-line a 6 mm lesion, volume 0.28 cm^3, is the smallest detectable. One explanation of the fact that much smaller abnormalities were detected in our study may be that a uniform distribution of radioactivity was used for the background image. Since there is no

TABLE II

SMALLEST SIZE OF CYLINDRICAL ABNORMALITY WHICH CAN BE DETECTED WHEN THE CONCENTRATION RATIO IS 22.5:1 AND THE BACKGROUND COUNT DENSITY IS THAT FOUND OVER CEREBRAL HEMISPHERES IN BRAIN SCANS PERFORMED IN ABERDEEN. THE SIZE OF THE ABNORMALITY IS EXPRESSED IN MM.

Imaging device	Count density over cerebral hemispheres cpe	Abnormality situated in air		Abnormality situated in 5 cm of Mix D	
		Depth of background tank, mm		Depth of background tank, mm	
		100	150	100	150
ASS	20	56 ± 2	58 ± 3	81 ± 3	88 ± 4
γ-camera	40	48 ± 2	55 ± 2	72 ± 3	79 ± 2
Elscint scanner	80	56 ± 2	60 ± 1	78 ± 1	83 ± 1

anatomical noise to obscure the abnormality it appears that the results of this study represent the smallest cylindrical abnormalities which could be detected with the imaging devices considered. Further data are required for spherical abnormalities.

Although it is possible to detect abnormalities whose sizes are much smaller than the collimator resolution, the size of the image on the display will reflect the collimator resolution rather than the true size of the abnormality. What has been considered in this paper is detection of abnormalities, *i.e.* being able to say that the image is abnormal, rather than recognition, *i.e.* accurate identification of the size and shape of the abnormality. The method does, however, permit an evaluation of the effectiveness of existing radiopharmaceuticals if small lesions are to be detected with current instrumentation.

REFERENCES

BECK, R. N., 1961. A theoretical evaluation of brain scanning systems. *Journal of Nuclear Medicine, 2,* 314–324.

BOWLEY, A. R., TAYLOR, C. G., CAUSER, D. A., BARBER, D. C., KEYES, W. I., UNDRILL, P. E., CORFIELD, J. R., and MALLARD, J. R., 1973. A radioisotope scanner for rectilinear, arc, transverse section and longitudinal section scanning (ASS- The Aberdeen Section Scanner). *British Journal of Radiology, 46,* 262–271.

CORSO, J. F., 1967. *The experimental psychology of sensory behaviour,* 229–236 (Holt, Rhinehart and Winston, New York).

DEWEY, W. C., and SINCLAIR, W. K., 1961. Criteria for evaluating collimators used in in-vivo distribution studies with radioisotopes. *International Journal of Applied Radiation and Isotopes, 10,* 1–16.

LAKSHMANAN, A. V., 1975. Ph.D Thesis, University of Aberdeen.

LAKSHMANAN, A. V., CAUSER, D. A., WILKS, R. J., TAYLOR, C. G., and MALLARD, J. R., 1975. A depth-independent collimator for use with ^{99}Tc^{m} in both conventional and transverse section scanning. *International Journal of Nuclear Medicine and Biology, 2,* 123–128.

MALLARD, J. R., and CORFIELD, J. R., 1969. A statistical test for the visualization of changes in the count density on radioisotopes scanning displays. *British Journal of Radiology, 42,* 530–538.

MALLARD, J. R., and WILKS, R. J., 1968. Characteristics of display systems in scanning and a simple phantom procedure to evaluate the overall scanner performance. *Journal of Nuclear Medicine, 9,* 96–109.

MATTHEWS, C. M. E., 1964, Comparison of coincidence counting and focusing collimators with various isotopes in brain tumour detection. *British Journal of Radiology, 37,* 531–543.

MCAFEE, J. G., and SUBRAMANIAN, G., 1975. Radioactive agents for imaging. In *Clinical Scintillation Imaging,* ed. Freeman, L. M. and Johnson, P. M. (Grune and Stratton, New York).

SCHULZ, A. G., KNOWLES, L. G., KOHLENSTEIN, L. C., MUCCI, R. F., and YATES, W. A., 1970. Quantitative assessment of scanning-system parameters. *Journal of Nuclear Medicine, 11,* 61–68.

SHARMA, R., and FOWLER, J. F., 1970. Threshold detection tests in radioisotope scanning. *Physics in Medicine and Biology, 2,* 289–300.

SHARP, P. F., 1976. Psychophysical assessment of the performance of clinical radioisotope imaging devices. In *Medical Images: Formation, Perception and Measurement,* ed. Hay, G. A. (The Institute of Physics and John Wiley and Sons).

SHARP, P. F., and MALLARD, J. R., 1974. A proposed model for the visual detection of signals in radioisotope display systems. *Physics in Medicine and Biology, 19,* 348–361.

1976. The measurement of the performance of the display system of a radioisotope imaging device: the multi-element band display. *British Journal of Radiology, 49,* 270–277.

1977. Measurement of the performance of the gamma camera oscilloscope display. *British Journal of Radiology, 50,* 822–824.

TELANDER, G. T., and LOKEN, M. K., 1967. Comparison of the scintillation camera with a rectilinear scanner using technetium-99m pertechnetate in a tumour brain phantom. *Journal of Nuclear Medicine, 9,* 96–109.

Book review

Invasive Radiologic Diagnostic Procedures. By Mary Kilduff Abbott, pp.ix+ 57, 28 illus., 1978 (Philadelphia, F. A. Davis Co.), $3.95.

This useful booklet, which covers an area previously sadly neglected, gives excellent descriptions of invasive radiological procedures, and the nurse's role in connnection with this work.

The American style of patient charting and care varies slightly from usual practices in this country, but not so much as to lessen the value of the book. U.K. contrast materials have different trade names (*e.g.* Renografin/Urografin). Individual radiologists have personal preferences as to method of work, and we believe the use of general anaesthesia is more common in the U.K., in particular with neuroradiology. Automatic injections are not always preferred to hand injections.

Altogether, a worth-while short introduction to angiography for the nurse in the X-ray department. She needs more help on all parts of her work, and a larger comprehensive text remains to be written.

R. J. FRANCE.
C. E. CLARKE.

1978, *British Journal of Radiology*, *51*, 992–996

The effect of chronic reductions in the arterial partial pressure of oxygen on the radiation response of an experimental tumour

By D. W. Siemann, B.Sc., R. P. Hill, B.A., Ph.D., and R. S. Bush, B.Sc., M.D., M.A., F.R.C.P.(C)

The Ontario Cancer Institute, incorporating the Princess Margaret Hospital, Toronto, M4X 1K9, Canada

(*Received January 1978 and in revised form May, 1978*)

Abstract

A previous study by the same authors has reported the effect of acute reductions in the arterial partial pressure of oxygen (PaO_2) on tumour response to radiation. The results have been extended in the present paper to investigate tumour response to radiation in animals in which the PaO_2 is chronically reduced. The purpose of these experiments was to simulate the condition of cancer patients undergoing radiotherapy in the presence of chronically low PaO_2 values as might be expected in patients with chronic respiratory disease. Mice bearing transplantable KHT sarcomas were kept in a 12% O_2 environment prior to (10–16 days), during and following the radiation treatment of their tumours. During the period of low PaO_2 (about 50 mm Hg) exposure, the mice were found to increase their haemoglobin (Hg) levels by approximately 50%. Because of this increase, the response, determined using a growth delay assay of the tumours irradiated at reduced PaO_2 was found to be the same as that observed for tumours in mice breathing air throughout the experiment. In mice with reduced PaO_2 levels maintained at normal Hb concentrations by periodic bleeding, tumour response was found to be similar to that of mice with acute PaO_2 reductions. These results indicate that chronic PaO_2 reductions in the absence of Hb compensation may have a detrimental effect on the success of a radiation treatment.

Alterations in the oxygen (O_2) distribution in a tumour due to changes in the quantity of O_2 carried in the blood may affect the response of the tumour to radiation. In retrospective clinical studies (Evans and Bergsjo, 1965; Hierlihy *et al.*, 1969; Taskinen, 1969; Bush, 1978) it has been shown that reduced blood haemoglobin (Hb) levels, such as are observed during anaemia, have an influence on the effectiveness of the radiation treatment. A recent prospective trial in carcinoma of the cervix (Bush, 1978) further indicates that transfusing patients to an Hb level above 12 g% prior to radiotherapy improves the local tumour control rate.

The quantity of O_2 carried in the blood depends however not only on the Hb concentration but also on the arterial partial pressure of O_2 (PaO_2). Reduced PaO_2 values have been observed under a variety of conditions, primarily as a result of respiratory impairments (Diament and Palmer, 1969; Davidson *et al.*, 1972). Because measurements at the Princess Margaret Hospital have indicated that some cancer patients may have reduced PaO_2 values, the KHT sarcoma was used in earlier experiments as a tumour model system to study the effect of acute reduction of PaO_2 on radiation response. The results (Siemann *et al.*, 1975) indicated that there is a linear relationship between PaO_2 and radiation-induced tumour growth delay for acutely reduced PaO_2 values. In patients, however, reductions of PaO_2 are usually due to chronic rather than acute changes. Consequently the question arises as to whether a tumour can adapt to a reduced PaO_2 during its growth such that its effective oxygenation is the same as that which would occur if the PaO_2 had been normal. This question has been examined in the same tumour model system used to study acute reductions of PaO_2, by inducing chronically low PaO_2 values (about 50 mm Hg) in tumour-bearing mice by keeping them in 12% O_2. The influence of such a reduction in PaO_2 tumour response to radiation was then determined using a growth-delay assay. The mice readily adapted to the reduced O_2 atmosphere by increasing their blood Hb concentration by a factor of about 1.5. Consequently the tumour response to radiation was studied both in mice with chronic low PaO_2 and increased Hb and in mice with chronic low PaO_2 values but in which normal Hb levels were maintained by periodic bleeding.

Materials and Methods

In these experiments, the KHT sarcoma (Kallman *et al.*, 1967) was transplanted into the right flank of 8 to 14 week-old C3H male mice by injecting 2×10^5 cells subcutaneously. Single cell suspensions for the transfer procedure were prepared as described previously (Thomson and Rauth, 1974). When the tumours had grown to a mean diameter of 5–6 mm, they were randomly allocated into a number of groups and irradiated or kept as controls as required. The radiation response of the tumours was determined using a growth delay assay (Thomlinson and Craddock, 1967; Siemann *et al.*, 1975) for five different treatment conditions:

(a) In mice kept at normal PaO_2 level (breathing air) before and after irradiation and at normal PaO_2 level during irradiation.

---

*Present address: University of Rochester Medical Center, Cancer Center, Box 704, 601 Elmwood Avenue, Rochester, New York, 14642, U.S.A.

(b) In mice kept at normal PaO_2 level before and after irradiation but at reduced PaO_2 level (breathing 13% O_2: 87% N_2) during irradiation.
(c) In mice kept at chronicly reduced PaO_2 level (in 12% O_2 chamber) before and after irradiation but at normal PaO_2 level (breathing air) during irradiation. These mice had above normal haemoglobin (Hb) levels.
(d) In mice kept at chronicly reduced PaO_2 level before and after irradiation and at reduced PaO_2 level (breathing 13% O_2: 87% N_2) during irradiation. These mice had above normal Hb levels.
(e) In mice kept at chronicly reduced PaO_2 level before and after irradiation and at reduced PaO_2 level during irradiation but periodically bled before irradiation to maintain a normal Hb level.

After the irradiation each tumour was measured daily along three perpendicular diameters, using calipers, and a "tumour volume" ($V=d_1\times d_2\times d_3/2$) calculated. The growth delay for a given radiation treatment was determined by the difference in the time required for the control and irradiated tumours to reach 365 mm³. This tumour size is equivalent to that used for the analysis in the previous study (Siemann *et al.*, 1975).

The chronic low PaO_2 values were obtained by keeping mice, housed in plastic cages (five per cage) with food and water *ad libitum*, in a reduced O_2 environment. Six such cages were inserted via an airlock into a chamber (250 litre) continuously flushed with a mixture of 10% O_2:90% N_2 at a rate of 80 litre/hour. The temperature and humidity in the chamber were maintained at 23–26°C and 40–80% respectively. The O_2 concentration in the chamber, determined by collecting a sample of the atmosphere in a glass syringe and analysing it in a blood-gas analyser, was found to be $12\%\pm1\%$. The level was routinely tested, indirectly, by determining the PaO_2 values of animals in the chamber. These PaO_2 values were found to remain constant throughout the exposure of the animals.

To maintain mice in the reduced O_2 atmosphere at normal Hb levels, the animals were bled (300–400 μl of blood from the orbital sinus) every second day commencing on the fourth day after entering the reduced O_2 environment, for a total of four to five bleedings. Immediately following each bleeding the mice were given an intraperitoneal injection of an equal volume of mouse serum. Hb measurements were made during the course of the bleedings to ensure that normal Hb values were maintained.

In the initial studies the mice were injected with tumour cells after six days of acclimatization in the chamber. In order to minimize the number of bleedings required to maintain normal Hb levels, in later experiments only one day of acclimatization was allowed prior to tumour cell injection. No difference in tumour growth or radiation response was observed between the two procedures.

All mice to be irradiated were anaesthetized with Nembutal (0.07 mg/g) and treated using a double-headed 100 kV X-ray unit at a dose-rate of 1140 rad/min as described previously (Siemann *et al.*, 1975). The irradiation commenced eight minutes after the injection and loss of body heat was prevented by keeping the anaesthetized animals wrapped in cotton wool at all times other than during the irradiation period. Animals maintained at chronic low PaO_2 were anaesthetized and placed into the radiation box while in the reduced O_2 environment and then transferred directly to the X-ray unit without being exposed to air. Upon completion of the irradiation the mice maintained at chronic low PaO_2 values prior to the treatment were immediately returned to the reduced O_2 environment.

The blood gas values were determined in mice in the reduced O_2 environment or in air under the same conditions as used for irradiation and using the method previously described (Siemann *et al.*, 1975). Briefly, a 100 μl blood sample was taken from the femoral artery and immediately analysed for PaO_2, $PaCO_2$, and pH using a blood-gas analyser. The Hb concentration in these samples was then determined spectrophotometrically (Crosby *et al.*, 1954).

RESULTS

Blood measurement

The PaO_2 values of mice kept in the low O_2 environment were found to fall rapidly to about 50 mm Hg within the first day and then remain constant. This value of PaO_2 is similar to those observed in mice placed acutely into 13% O_2:87% N_2 (Siemann *et al.*, 1975); consequently, the mice were given this gas mixture to breathe to maintain low PaO_2 conditions during irradiation of their tumours. Actually animals chronically exposed to 12% O_2 possess somewhat higher PaO_2 values while breathing 13% O_2:87% N_2 than do air-breathing mice acutely exposed to this gas mixture (Table I). Previous findings indicate, however, that this small difference in PaO_2 at the time of irradiation is unlikely to result in a detectable change in tumour growth delay (Siemann *et al.*, 1975).

The effect on the Hb levels of continuous exposure to a 12% O_2 environment is illustrated in Fig. 1 (solid squares). Hb data for air-breathing mice are shown for comparison (solid circles). It can be seen

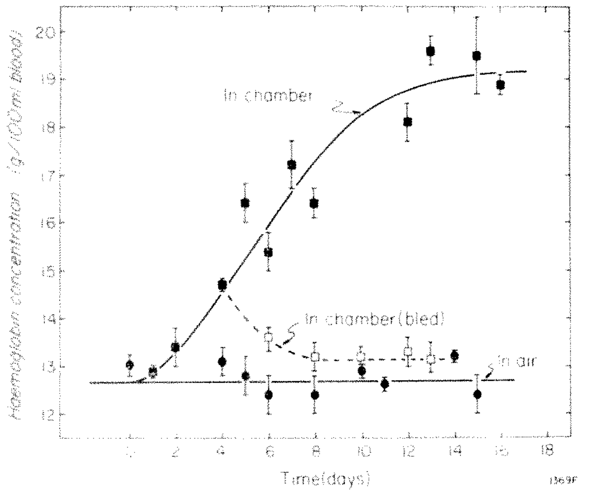


FIG. 1.

Haemoglobin concentration as a function of time in mice exposed to a 12% O_2 environment. Results for animals which adapted to the environment (solid squares) and mice whose haemoglobin levels were reduced by periodic bleeding (open squares) are illustrated. Haemoglobin levels of air-breathing mice are shown for comparison (closed circles). All data are the mean of 5–35 animals ± standard error.

that the Hb concentrations increased as a function of time spent in the chamber and reached a value of about 19 g/100 ml of blood, 12–14 days after the mice entered the reduced O_2 environment. Note that at the time of irradiation of the tumours (day 10–13), the Hb levels of the mice with chronic low PaO_2 values had risen by a factor of about 1.5 above normal. Animals kept in the low O_2 atmosphere but bled on alternate days (open squares) could be maintained, however, at Hb levels similar to those of air-breathing mice.

Response of tumours to irradiation

Figure 2 shows tumour volume as a function of time after a single dose of 1500 rad for mice irradiated while breathing 13% O_2:87% N_2 or air (experiment 5 of Table I). The results for animals kept in air or in 12% O_2 in the chamber prior to irradiation are illustrated in the upper and lower panel respectively. The mice maintained in the reduced O_2 environment (lower panel) were either not bled (closed squares) and consequently had Hb values at the time of irradiation considerably elevated above normal (Fig. 1) or were bled (closed circles) and had normal Hb levels. The results indicate that mice with chronic PaO_2 reduction but an increased Hb level exhibit the same tumour growth delay as air-breathing animals not exposed to the low O_2 environment (solid squares *vs* open squares). However, chronic PaO_2 reductions in mice kept at normal Hb concentrations lead to a tumour response similar to that observed in mice whose PaO_2 values had been reduced acutely (solid circles *vs* open circles).

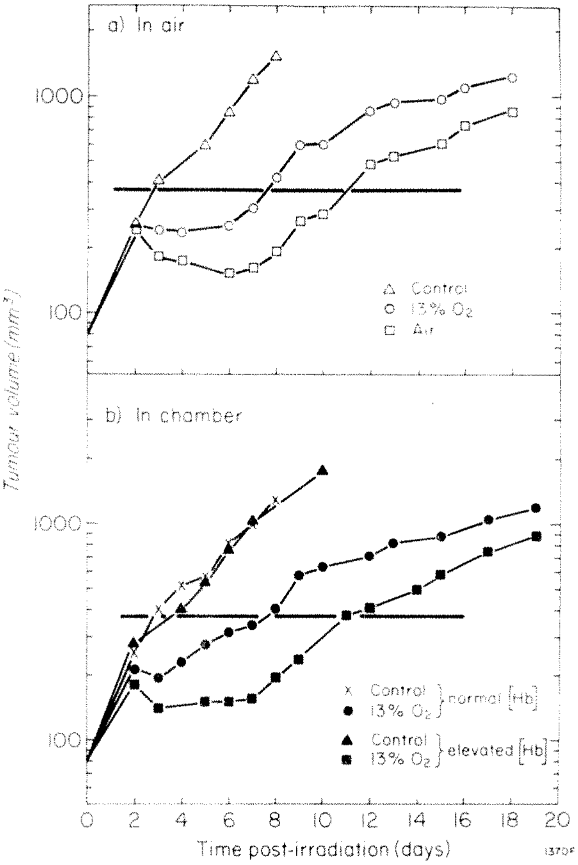


FIG. 2.

Tumour response of Nembutal-anaesthetized mice to a single dose of 1500 rad. (a) Mice kept in air and irradiated at normal (open squares) or acutely reduced (open circles) PaO_2 values. (b) Mice kept at 12% O_2 with chronic PaO_2 reductions irradiated in the presence of normal (closed circles) or elevated (closed squares), haemoglobin concentrations. All data points are the mean of 5–6 mice.

These experiments have been repeated a number of times and a summary of all the growth-delay data is shown in Table I. The data obtained in the present study for mice with normal or acutely reduced PaO_2 values (experiments two to six) compare favourable with those published previously (Siemann *et al.*, 1975) which are given in the table as experiment one. Although there is some variability in the results from experiment to experiment (particularly experiment six), within experiments the points demonstrated in Fig. 2 are found to be reproducible. Statistical

TABLE I

TUMOUR GROWTH DELAYS (DAYS) FOLLOWING A SINGLE DOSE OF 1500 RAD AS A FUNCTION OF PaO_2 IN MICE WITH NORMAL OR RAISED HB VALUES

Gas breathed before and after irradiation	Air		$12\% O_2 : 88\% N_2$		
Haemoglobin level	Normal		Raised		Normal
PaO_2 during irradiation (mm Hg)*	95.7 ±1.1	51.8 ±1.3	95.9 ±0.8	55.2 ±2.0	55.2 ±2.0
	(a)	(b)	(c)	(d)	(e)
Expt. 1	7	4–5	—	—	—
2	7	5	9	7	—
3	8	5	—	8	—
4	6	—	8	—	—
5	8	5	—	8	5
6	11	7	—	10	7

*Data are the mean of at least five measurements ± S.E. Mice breathed either air (columns (a) and (c)) or $13\% O_2$: $87\% N_2$ (columns (b), (d) and (e)) for three minutes prior to blood sampling to allow the PaO_2 to reach equilibrium (Siemann *et al.*, 1975).

analysis using the Wilcoxon (Mann-Whitney) ranking test (Snedecor and Cochran, 1973) indicates a significant difference (p less than 0.05) between the tumour response of air-breathing mice and of animals with chronic PaO_2 reductions and normal Hb levels (experiments five and six column (a) *vs* (e)). No difference was found between the response of tumours in air-breathing animals and those in mice with chronic PaO_2 reductions and raised Hb levels (column (a) *vs* (d)).

DISCUSSION

In this study, chronically low values of PaO_2 were produced by placing healthy C3H mice into an atmosphere containing $12\% O_2$. Introducing animals into such an atmosphere not only lowers the PaO_2 to about 50 mm Hg but also reduces the percentage saturation of the Hb to about 70% (Gray and Steadman, 1964). The mice adapted to this environment by increasing their Hb concentrations (Fig. 1) and possibly by an increase in alveolar ventilation as is observed in man upon exposure to high altitude (Frisancho, 1975). The latter is suggested by the difference in PaO_2 values observed when air-breathing mice or animals maintained at chronically low PaO_2 are acutely exposed to $13\% O_2{:}87\% N_2$ (Table I). Hyperventilation would allow the animals in the low O_2 environment to maintain higher arterial O_2 tension while breathing a gas mixture with a reduced content of O_2. The measured differences in PaO_2 probably reflect minimum changes in ventilation because the values were obtained from mice anaesthetized by Nembutal which is known to depress respiration (Kruuv *et al.*, 1967). However, since the radiation experiments were carried out under identical conditions to the blood-gas measurements, it is likely that hyperventilation has very little influence on the observed tumour response to radiation.

During their stay in the reduced O_2 atmosphere the animals had an initial loss in body weight; although both these mice and the air-breathing animals were injected with an identical number of tumour cells at the start of the experiment, it required an extra day for the tumours in the mice kept at low O_2 to reach the treatment size. Nevertheless, once established, the tumours of all the unirradiated control groups showed very similar growth curves (Fig. 2). These observations are in qualitative agreement with those of Tannock (1968) who studied tumours growing in rats exposed to a $10\% O_2$ environment.

The results in Fig. 2 and Table I demonstrate that the response of the tumour to radiation is critically related to the PaO_2 and blood Hb concentration at the time of irradiation. Tumours irradiated in mice which were allowed to adapt to a chronic PaO_2 reduction by increasing their Hb level (columns (c) and (d), Table I) demonstrate a greater growth delay than tumours in mice exposed to a similar PaO_2 level acutely (columns (a) and (b), Table I). Since changes in the blood Hb concentration can alter tumour response to radiation (Hill *et al.*, 1971), it seems likely that the observed increase in Hb level of the mice kept in the chamber (Fig. 1) accounts for the greater growth delay observed for chronic as opposed to acute reductions in PaO_2. This conclusion is supported by the finding that tumours in mice maintained at chronically low PaO_2 values but kept at a normal blood Hb concentration exhibit a growth delay about three days less than that found for tumours in air-breathing mice (Fig. 2, open squares *vs* closed circles and column (e) *vs* (a), Table I). This difference in delay is similar to that observed for an acute reduction in PaO_2 at the time of irradiation (Fig. 2, open squares *vs* open circles and column (e) *vs* (b), Table I). Thus the results indicate that a reduction in PaO_2 leads to a reduced tumour response to radiation unless it is compensated by an increase in the blood Hb level.

CONCLUSIONS

This study was designed to investigate whether chronic respiratory disease leading to reduced values of PaO_2 in cancer patients has a detrimental effect on the radiation response of their tumours. To simulate this situation the response to radiation of tumours in mice kept in a 12% O_2 environment during tumour growth was examined. The chronically low PaO_2 values obtained in these experiments clearly arise in a different manner from those in patients with lung disease. Nevertheless, it is hoped that this investigation may serve as a model for the effect of low PaO_2 values on tumour response to radiation. Significantly reduced PaO_2 values may occur in patients who are to be treated for cure by radiation therapy. Reduced PaO_2 values in man are, however, often not associated with compensatory increases in Hb (Davidson *et al.*, 1972). The results presented here imply that the prognosis for such patients may be worse than that for patients with similar tumours but normal PaO_2 values when treated with radiation. Positive steps to eliminate all factors which reduce tumour oxygenation, such as anaemia, low PaO_2 values or high carboxy-Hb levels (Siemann *et al.*, 1978), during radiation therapy might well result in an improvement in tumour control at the local treatment site.

Acknowledgments

This work was supported by a grant from the Ontario Cancer Treatment and Research Foundation. One of us (D.W.S.) was the recipient of a Studentship from the Medical Research Council of Canada. The authors thank Dr. A. M. Rauth for his constructive criticism of the manuscript.

REFERENCES

Bush, R. S., 1978. Definitive evidence for hypoxic cells influencing cure in cancer therapy. *British Journal of Cancer*, *37*, Suppl. III, 302–306.

Crosby, W. H., Munn, J. I., and Furth, F. W., 1954. Standardizing a method for clinical hemoglobinometry. *United States Armed Forces Medical Journal*, *5*, 693.

Davidson, F. F., Glazier, J. B., and Murray, J. F., 1972. The components of the alveolar-arterial oxygen tension difference in normal subjects and in patients with pneumonia and obstructive lung disease. *American Journal of Medicine*, *52*, 754–762.

Diament, M. L., and Palmer, K. N. V., 1969. An analysis of pre-operative PaO_2 in a general surgical population. *Thorax*, *24*, 126–128.

Evans, J. C., and Bergsjo, P., 1965. Influence of anemia on the results of radiotherapy in carcinoma of the cervix. *Radiology*, *84*, 709–716.

Frisancho, A. R., 1975. Functional adaptation to high altitude hypoxia. *Science*, *187*, 313–319.

Gray, L. H., and Steadman, J. M., 1964. Determination of the oxyhaemoglobin dissociation curves for mouse and rat blood. *Journal of Physiology (London)*, *175*, 151–171.

Hierlihy, P., Jenkin, R. D. T., and Stryker, J. A., 1969. Anemia as a prognostic factor in cancer of the cervix: a preliminary report. *Canadian Medical Association Journal*, *100*, 1100–1102.

Hill, R. P., Bush, R. S., and Yeung, P., 1971. The effect of anaemia on the fraction of hypoxic cells in an experimental tumour. *British Journal of Radiology*, *44*, 299–304.

Kallman, R. F., Silini, G., and Van Putten, L. M., 1967. Factors influencing the quantitative estimation of the *in vivo* survival of cells from solid tumours. *Journal of the National Cancer Institute*, *39*, 539–549.

Kruuv, J. A., Inch, W. R., and McCredie, J. A., 1967. Blood flow and oxygenation of tumors in mice. I. Effects of breathing gases containing carbon dioxide at atmospheric pressure. *Cancer*, *20*, 51–59.

Siemann, D. W., Bronskill, M. J., Hill, R. P., and Bush, R. S., 1975. The relationship between mouse arterial partial pressure of oxygen (PaO_2) and the effectiveness of localized tumour irradiation. *British Journal of Radiology*, *48*, 662–667.

Siemann, D. W., Hill, R. P., and Bush, R. S., 1978. Smoking: the influence of carboxyhemoglobin (HbCO) on tumour oxygenation and response to radiation. *International Journal of Radiation Oncology, Biology and Physics*, *4*, 657–662.

Snedecor, G. W., and Cochran, W. G., 1973. *Statistical Methods.* Sixth ed. (The Iowa State University Press, Ames, Iowa).

Tannock, I. F., 1968. The relationship between cell proliferation and the vascular system in a transplanted mouse mammary tumour. *British Cancer of Cancer*, *22*, 258–273.

Taskinen, P. J., 1969. Radiotherapy and TNM classification of cancer of the larynx. *Acta Radiologica Supplement*, *287*.

Thomlinson, R. H., and Craddock, E. A., 1967. The gross response of an experimental tumour to single doses of X rays. *British Journal of Cancer*, *21*, 108–123.

Thomson, J. E., and Rauth, A. M., 1974. An *in vitro* assay to measure the viability of KHT tumor cells not previously exposed to culture conditions. *Radiation Research*, *58*, 262–276.

Book review

Acoustic instrumentation and characterization of lung tissue. By T. L. Rhyne. Ultrasound in Biomedicine Series, Vol. 2, pp. 107, 1977 (Research Studies Press, Forest Grove, U.S.A.), $14.95.

The above book reviewed in The British Journal of Radiology, August 1978, page 621 may be obtained from Research Studies Press, 8 Willian Way, Letchworth, Herts SG6 2HG, U.K. at a price of £10·80.

1978, *British Journal of Radiology*, *51*, 997–1002 DECEMBER 1978

The effect of vascular occlusion on the thermal sensitization of a mouse tumour

By Sally A. Hill, M.Sc., and Juliana Denekamp, Ph.D.

Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

(*Received February, 1978 and in revised form June, 1978*)

ABSTRACT

The effect of occluding the blood supply to a mouse tumour (with a metal clamp) has been studied for both irradiation and heating. Local heat was applied by immersion in a water bath for one hour at 42.8°C or for 15 minutes at 44.8°C.

Occlusion of the blood supply during heating has a profound cytotoxic effect on the tumour, even in the absence of irradiation. Most tumours treated with 42.8°C for one hour under clamped conditions were locally controlled whether they were irradiated or not. Tumours heated with their blood supply unobstructed showed a lesser sensitivity to heat, seen as an increased sensitivity to X rays with a thermal enhancement ratio of 1.8–2.6.

With the shorter period of more intense heat (44.8°C for 15 min), the effect of increasing the clamping time before heating was studied. The proportion of tumours locally controlled increased from 33% if the clamp was applied immediately before heating to 83% if the clamp was present for 60 minutes before heating commenced. No cures were observed for heat applied immediately before clamping, or immediately after release of the clamp. Accumulation of metabolic products or pH changes are implicated as the factors which alter the thermal sensitivity of these tumour cells.

Several *in vitro* studies have shown a greater thermal sensitivity of hypoxic cells than of aerobic cells. This effect has been demonstrated for cell killing produced by heat alone (*e.g.* Kim, *et al.*, 1975a; Gerweck *et al.*, 1974; Harisiadis *et al.*, 1975), and in combination with X rays, in which case heating caused a reduction in the oxygen enhancement ratio (Kim, *et al.*, 1975b; Robinson *et al.*, 1974). However such studies may be complicated by the method used to produce the hypoxia (Schulman and Hall, 1974), as both nutritional deficiency and low pH have been shown to increase the sensitivity of cells to hyperthermia (Hahn, 1974; Overgaard and Overgaard, 1975; Gerweck and Rottinger, 1976). Further studies have indicated that, *in vitro*, pH may be more important than hypoxia itself (Gerweck, 1977; Overgaard & Bichel, 1977). Dewey and co-workers have also shown, *in vivo*, that chronically hypoxic tumour cells are much more sensitive to heat than cells made acutely hypoxic for the heat treatment (Dewey *et al.*, 1977; Thrall *et al.*, 1975).

The present investigation examines the effect of heat on solid subcutaneous tumours, clamped to occlude the blood supply and thus to render the normally oxygenated cells acutely hypoxic. In this situation depletion of nutrients, accumulation of waste products and pH changes might all contribute to the tumour response. Three types of experiment have been performed.

1. The tumours have been clamped before and during irradiation in order to make the cells uniformly radioresistant, but the heat (one hour at 42.8°C) has been applied to unclamped tumours.
2. The tumours have been clamped to occlude their blood supply for both heating (42.8°C for one hour) and irradiation.
3. A shorter period of more intense heat (44.8°C for 15 minutes) has been applied at different positions within an 80 minute period of clamping, without any irradiation.

MATERIALS AND METHODS

The tumour used for this study was an anaplastic derivative of a squamous carcinoma of the skin (squamous carcinoma "D") which arose spontaneously in Dr. H. B. Hewitt's colony of WHT mice in 1965. The origin and some of the radiobiological properties of the tumour have been described previously (Hewitt, *et al.*, 1967; Hill and Fowler, 1977b).

The tumours were implanted subcutaneously by trocar, on the ventral wall of the thorax. They were selected for treatment 7–20 days later, when they reached a mean diameter of between 5.0 and 6.5 mm. The volume doubling time was then approximately two days.

Tumour irradiations were performed as previously described (Fowler *et al.*, 1975), using 240 kV X rays (0.25 mm Cu+1 mm Al filter; HVL 1.3 mm Cu; 2.4 Gy/min). The mice were anaesthetized with 60 mg/kg sodium pentobarbitone and irradiated while breathing air at room temperature. An additional "top-up" dose of 10–20 mg/kg was given as necessary to maintain prolonged anaesthesia in the heated mice. The blood supply to the tumour was occluded by applying a D-shaped metal clamp across the base of the tumour ten minutes before treatment. The treatments given are listed in Table I. Local heat was administered by immersion of the tumours in water in a thermostatically controlled water bath with a temperature variation not greater than 0.05°C. A water-bath temperature of 42.8°C produced a measured intra-tumour temperature of 42.5°C, with no significant variation ($\leqslant 0.1$°C) across the tumour diameter, within 5–15 minutes of immersion in sample unclamped tumours tested with a thermocouple probe. In clamped tumours, the temperature rose more rapidly and more closely approached the temperature of the water. Within 2–5 minutes of immersion the intra-tumour temperature was within 0.2°C of the water bath temperature and finally stabilized between 0 and 0.1°C below it. Heating was always for a total period of 60 minutes immersion, and was given either immediately before or after the X-ray dose.

After treatment, tumours were measured with vernier calipers three times per week in three perpendicular dimensions, until they reached 12 mm mean diameter, at which time the mice were killed. The number of days taken to grow from 5.5 to 10 mm mean diameter (approximately two volume doublings) was calculated for each tumour and plotted against the dose of X rays.

Results and Conclusions

Figure 1 shows the response of tumours irradiated ten minutes after occluding the blood supply with a clamp (no heat). Each open circle represents an individual tumour; the mean and standard error of the mean for each dose group is also shown (closed circles).

TABLE I

Summary of experimental protocols

Controls		Details	Effect
C	clamp alone	clamp for 80 minutes	none
X^c	clamp + X rays	clamp for ten minutes before and during irradiation	—
△	heat alone	heat by immersion in waterbath at 42.8°C/1 hour	none
$△^c$	clamp & heat	clamp ten minutes before and during 60 minutes heating	large
Aerobic heat and clamped irradiation			
$△+X^c$	heat first	heat (one hour unclamped) then clamp ten minutes before and during irradiation	some
$△+X^c$	heat first	as above but clamp applied for last ten minutes in waterbath, followed immediately by irradiation	some
$X^c+△$	heat last	clamp ten minutes before and during irradiation; clamp off and then heat for one hour	some
Clamped heat and clamped X-irradiation			
$△^c+X^c$	heat first	clamp ten minutes before and during one hour in waterbath, and during irradiation	large
$X^c+△^c$	heat last	clamp ten minutes before and during irradiation and during one hour in waterbath	large

The duration of X irradiation ranged from 3–20 minutes, depending upon the X-ray dose.

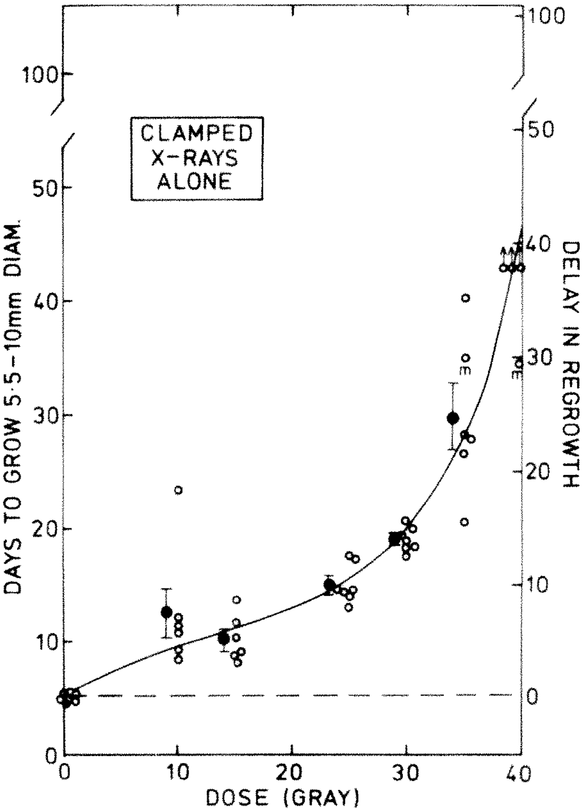


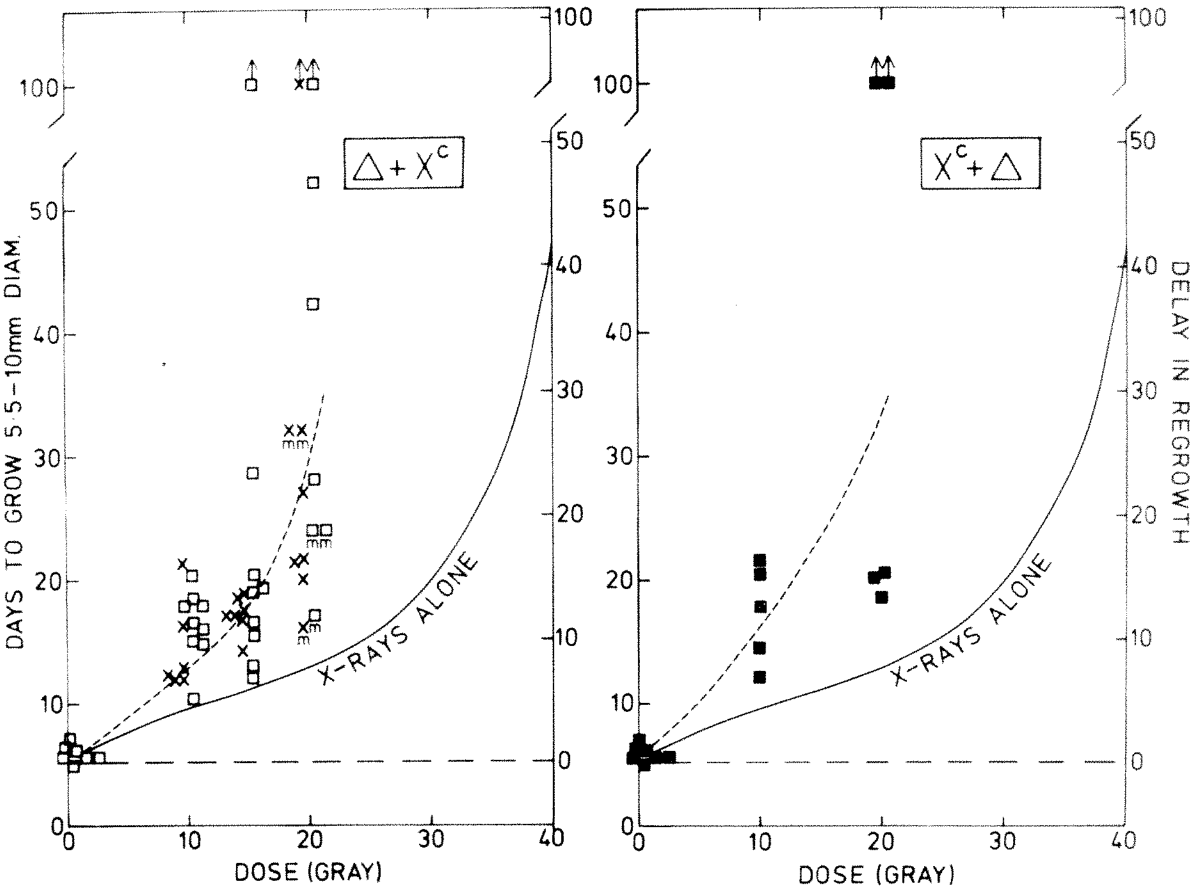
Fig. 1.

Growth delay of squamous carcinoma "D" treated with X rays alone under clamped conditions. ○ = individual tumours irradiated ten minutes after occluding the blood supply with a clamp. ● = mean ± standard error of the mean for each dose group. m = animal killed owing to development of metastases before regrowth of primary tumour.

The points at zero dose show that no delay is caused by clamping the tumours for 80 minutes without the addition of X rays. The mean number of days for clamped tumours to grow from 5.5 to 10 mm was 5.16±0.13 days, compared with 5.72±0.4 days for untreated tumours. The solid curve has been drawn by eye through the data. The application of the clamp was shown previously to make the tumours more radioresistent than those irradiated in air (Hill and Fowler, 1977a).

Figures 2 and 3 show the increased tumour response if the tumours were heated before or after irradiation. A much greater effect was observed if the tumours were clamped for *both* heat and irradiation (Fig. 3) than if they were clamped for the irradiation alone (Fig. 2).

Figure 2 shows the response to aerobic heating and irradiation while clamped. A considerable increase in tumour delay was observed at all dose levels, whether the heat was given before (Fig. 2A) or after (Fig. 2B) irradiation. No significant delay was observed at zero dose for tumours heated for one hour at 42.8°C without irradiation. When heat was applied first, and the tumours were to be clamped for ten minutes before irradiation, two possible schedules were possible: either the clamp could be



A

B

FIG. 2.

Moderate effect of heat given under aerobic conditions with X rays given to clamped tumours. Growth delay versus X-ray dose. The solid line is redrawn from Fig. 1 for X rays alone.

(A) Heat *before* irradiation. All heated tumours show a greater delay than the mean of those treated with X rays alone.
X = clamp applied after the heating period
□ = clamp applied during last 10 minutes in the waterbath
TER = 1.8–2.0
m = premature killing due to metastases, as in Fig. 1.

(B) Heat *after* irradiation. The heated tumours show a greater delay than the mean of those treated with X rays alone.
TER = 1.8–2.6.

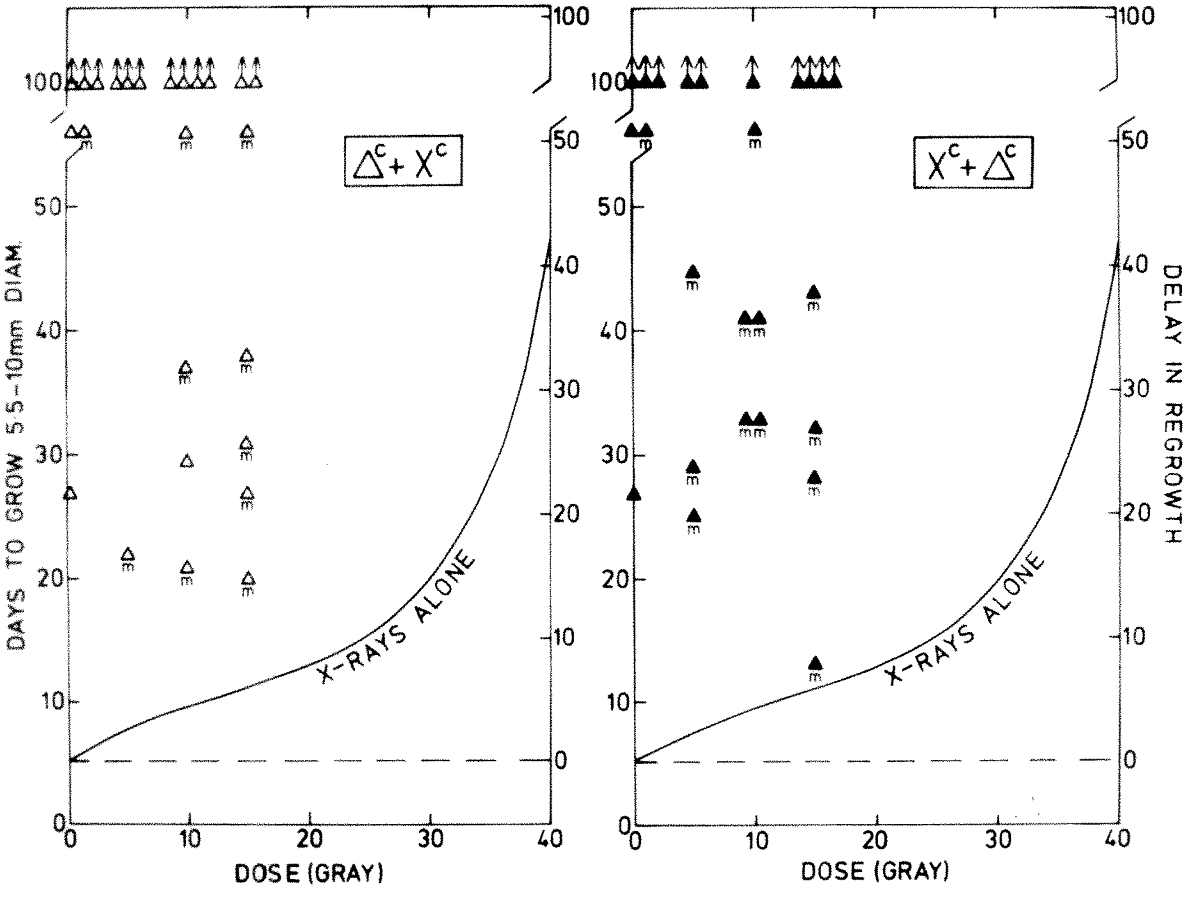


FIG. 3.

Large effect of heat added to X rays, when both were given to clamped tumours. Growth delay versus X-ray dose; the solid line is redrawn from Fig. 1.

(A) Heat *before* irradiation. Most tumours are locally controlled at 50–100 days. m = premature killing due to development of metastases, as in Fig. 1.

(B) Heat *after* irradiation. Most tumours are locally controlled at 50–100 days.

applied after the 60 minute immersion in the water bath and a ten minute gap would occur before the X rays were given (X), or the clamp could be applied for the last ten minutes in the water bath (☐), so that the X rays were given within two minutes of heat. Both techniques were used and there is no significant difference between the two sets of data (Fig. 2A).

The dashed lines in Figs. 2A and 2B have been drawn by eye through the average response of each dose group. This enables a quantitative estimate of thermal enhancement ratio (TER)* to be derived from the X-ray doses needed to give the same effect. The TER values are 1.8–2.0 for pre-treatment with heat and 1.8–2.6 for post-treatment. These values are somewhat, but not significantly, higher than those previously obtained when both heat and irradiation were given to aerobic tumours (Hill and Fowler, 1977b).

Figure 3 shows the response of tumours clamped for *both* the irradiation and the heating period. In these clamped tumours heat alone (zero dose) produced very prolonged growth delay, with 5/6 tumours being locally controlled at 50–100 days. When radiation doses of 5–15 Gy were added all but one of the tumours were locally controlled, either at 100

---

*TER = $\frac{\text{X-ray dose without heat}}{\text{X-ray dose with heat}}$ to give the same measure of damage.

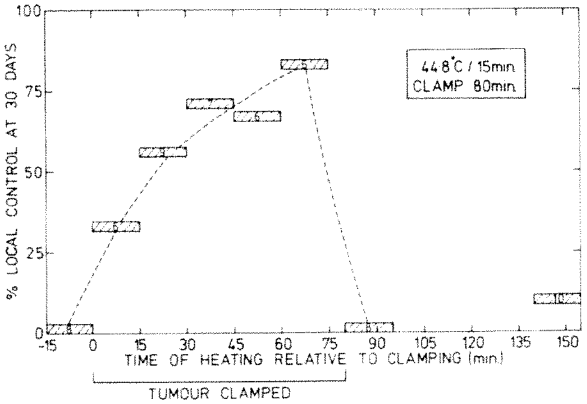


FIG. 4.

Local tumour control at 30 days for tumours heated (44.8°C for 15 minutes) at various times before, during or after the application of a clamp for 80 minutes. No X rays were given. The number in each bar represents the number of mice surviving for analysis at 30 days (see text).

days or at the time when the animals were sacrificed because of pulmonary metastases (marked m). The effect was similar whether heat was given before, after or without irradiation.

It is not possible from Fig. 3 to estimate a thermal enhancement ratio for sensitization to X rays, since heat alone in these clamped tumours is at least as effective as 40 gray given to clamped tumours without heating. A comparison of Figs. 2 and 3 demonstrates the enormous additional effect resulting from the occlusion of the blood supply during the period of heating. The initial response of tumours treated in this way was also qualitatively different. They regressed much more rapidly than after other treatments, forming flat black scabs which eventually fell off and did not regrow, or which remained while regrowth occurred from the margins.

These results agree with the observations of Crile (1963) and Suit (1977) who described an increase in the effectiveness of hyperthermia under clamped conditions. Thrall *et al.* (1975) however, reported no significant difference for local control of a C_3H mammary carcinoma between a heat dose of 44.5°C for 15 min given under ambient or hypoxic conditions immediately before acutely hypoxic irradiations. Two other tumours, a mammary carcinoma CBA NT and a fibrosarcoma have also been tested in our laboratory (Hill and Stewart, unpublished data). The results are similar to those reported here for the squamous carcinoma "D". The regrowth delay is significantly increased when moderate hyperthermia is applied under clamped conditions.

Figure 4 shows the result of an experiment in which the thermal insult was produced with a temperature two degrees higher for one-quarter of the time. Tumours were immersed in a water bath set at 44.8°C for 15 minutes, at various times before, during and after the 80 minute period of clamping. Ten to fourteen mice were treated at each time interval, but up to half of these were lost within 30 days because of lung metastases. The results are presented as the percent of animals in which the primary tumour was locally controlled at 30 days after treatment. Although this is an early time to score local control we know that for the squamous carcinoma "D" most recurrences are obvious by this time. Some animals were cured in all the treatments where the heat was given to a clamped tumour, but the local control rate increased as the interval between applying the clamp and immersing in hot water was increased. Five out of six tumours were "cured" when the heat was given during the last 15 minutes of clamping. No "cures" were achieved when heat was given immediately before clamping or immediately after releasing the clamp.

The response shown in Fig. 4 could result from hypoxia, nutrient depletion, metabolite accumulation or pH changes. It could also result from a loss of the cooling effect of flowing blood. However the latter effect should be constant throughout the period when the blood supply is totally occluded. Also, radiobiological hypoxia can be achieved very quickly by cellular respiration *in vivo*, *e.g.* within 20–30 seconds in mouse skin (Denekamp *et al.*, 1974). Thus, the increasing effect as the pre-treatment under clamped conditions is lengthened suggests that hypoxia and heat dissipation are less important than the other factors.

Metastases

The large number of animals killed because of pulmonary metastases (Fig. 3) suggested at first that the heat treatment may have increased the incidence of distant metastatic spread. This suggestion was not supported by a retrospective analysis of all the data. The incidence of lung metastases was 35% in animals treated with single doses of X rays alone under ambient conditions (unpublished data). The incidence of about 50% in Figs. 3A and 3B was not significantly different from that in unheated mice and the metastases occurred over a similar time span. Because the primary tumours were controlled better with heat more animals survived long enough to develop clinical symptoms of metastases. It is clear that local heating of the implanted tumour did not prevent the growth of microscopic deposits of tumour elsewhere in the body. The incidence and rate of development of metastases in irradiated and in heated mice is currently under more detailed investigation.

Conclusion

Occlusion of the blood supply during application of moderate hyperthermia (by immersion in a water bath at 42.8°C for one hour or 44.8°C for 15 minutes) had a profound effect on the cytotoxicity of the heat treatment. Heat alone to clamped tumours was as effective as 40 gray of X rays given without heat. Inadvertent restriction of the blood supply when applying heat in other studies of hyperthermic radiosensitization of tumours could, we believe, result in *artificially* large thermal enhancement ratios. These could give the false impression of a therapeutic advantage of combined heat and radiation that would not be maintained in a non-clamped clinical situation. The increased thermal sensitivity in clamped tumours seems likely to result from reduced pH and/or build up of metabolic waste products, rather than from simple hypoxia or the inability to dissipate heat via the vasculature.

Acknowledgments

We would like to thank Prof. J. F. Fowler, Dr. S. B. Field and Miss F. A. Stewart for their constructive criticism of this manuscript and Mrs. Lynda Hall and her staff for the production and maintenance of the animals. We are grateful to the Cancer Research Campaign for their support of this work.

REFERENCES

Crile, G., 1963. The effects of heat and radiation on cancers implanted on the feet of mice. *Cancer Research*, *23*, 372–380.

Denekamp, J., Michael, B. D., and Harris, S. R., 1974. Hypoxic cell radiosensitizers: comparative tests of some electron affinic compounds using epidermal cell survival *in vivo*. *Radiation Research*, *60*, 119–132.

Dewey, W. C., Thrall, D. E., and Gillette, E. L., 1977. Hyperthermia and radiation—a selective thermal effect on chronically hypoxic tumour cells *in vivo*. *International Journal of Radiation Oncology, Biology and Physics*, *2*, 99–103.

Fowler, J. F., Sheldon, P. W., Begg, A. C., Hill, S. A., and Smith, A. M., 1975. Biological properties and response to X rays of first-generation transplants of spontaneous mammary carcinomas in C3H mice. *International Journal of Radiation Biology*, *27*, 463–480.

Gerweck, L. E., 1977. The lethal response of cells to radiation or hyperthermia under acute and chronic hypoxic conditions: (abstract). *Radiation Research*, *70*, 612.

Gerweck, L. E., Gillette, E. L., and Dewey, W. C., 1974. Killing of Chinese hamster cells *in vitro* by heating under hypoxic or aerobic conditions. *European Journal of Cancer*, *10*, 691–693.

Gerweck, L. E., and Rottinger, E., 1976. Enhancement of mammalian cell sensitivity to hyperthermia by pH alteration. *Radiation Research*, *67*, 508–511.

Hahn, G. M., 1974. Metabolic aspects of the role of hyperthermia in mammalian cell inactivation and their possible relevance to cancer treatment. *Cancer Research*, *34*, 3117–3123.

Harisiadis, L., Hall, E. J., Kraljevic, V., and Borek, C., 1975. Hyperthermia: biological studies at the cellular level. *Radiology*, *117*, 447–452.

Hewitt, H. B., Chan, D., and Blake, E., 1967. Survival curves for clonogenic cells of a murine keratinizing squamous carcinoma irradiated *in vivo* or under hypoxic conditions. *International Journal of Radiation Biology*, *12*, 535–549.

Hill, S. A., and Fowler, J. F., 1977a. Radiosensitizing and cytocidal effects on hypoxic cells of Ro-07-0582, and repair of X ray injury, in an experimental mouse tumour. *British Journal of Cancer*, *35*, 461–469.

1977b. Combined effect of heat and X rays on two types of mouse tumour. Proceedings of 2nd International Symposium on Cancer Therapy by Hyperthermia and Radiation, June 2–4, Essen, Germany. Eds. Streffer *et al.*, (Urban and Schwarzenberg, Munich), pp. 251–252.

Kim, S. H., Kim, J. H., and Hahn, E. W., 1975a. Enhanced killing of hypoxic tumour cells by hyperthermia. *British Journal of Radiology*, *48*, 872–874.

1975b. The radiosensitization of hypoxic tumour cells by hyperthermia. *Radiology*, *114*, 727–728

Overgaard, J., and Bichel, P., 1977. The influence of hypoxia and acidity on the hyperthermic response of malignant cells *in vitro*. *Radiology*, *123*, 511–514.

Overgaard, J., and Overgaard, K., 1975. Effect of environmental acidity on the hyperthermic treatment of tumour cells. *IRCS Medical Science: Biochemistry; Cancer; Cell and Membrane Biology*, *3*, 386.

Robinson, J. E., Wizenberg, M. J., and McCready, W. A., 1974. Combined hyperthermia and radiation suggest an alternative to heavy particle therapy for reduced oxygen enhancement ratios. *Nature*, *251*, 521–522.

Schulman, N., and Hall, E. J., 1974. Hyperthermia: its effect on proliferative and plateau phase cell cultures. *Radiology*, *113*, 207–209.

Suit, H. D., 1977. Hyperthermic effects on animal tissues. *Radiology*, *123*, 483–487.

Thrall, D. E., Gillette, E. L., and Dewey, W. C., 1975. Effect of heat and ionizing radiation on normal and neoplastic tissue of the C3H mouse. *Radiation Research*, *63*, 363–377.

1978, *British Journal of Radiology*, *51*, 1003–1004

Instrumental and technical notes

Automatic numbering punch for radiation protection films

By K. P. Goulding and F. W. Walton

Department of Medical Physics, Royal South Hants Hospital, Graham Road, Southampton

(Received April, 1978 and in revised form July, 1978)

A new design of press is described, the operation of which allows for automatic numbering and collection of films. The system is completely pneumatic and supersedes the mechanical toggle press previously in use.

The main reason for designing a new system was that numbers on the films were difficult to identify after processing because of the change of Kodak RP film from acetate to polyester film base. A policy decision was made to replace the mechanical press and enquiries from other NHS Film Badge Services revealed that the majority of machines in use did not give completely satisfactory results. It was decided to manufacture a machine based on a new concept using fluid power.

Our first stage was to evaluate what was required, bearing in mind the dimensional variation of the wrapped films. The results of this evaluation identified the following criteria:

(1) satisfactory marking of the film;
(2) automatic feed of the film to the head;
(3) automatic collection of the film from the head;
(4) consistently accurate machine parameters.

Design

A Shraeder $\frac{1}{2}$ ton (500 kg) double-acting press was used as the basis for the design. Air cylinders (2.5 cm bore) of selected stroke are used to position the film at the various stages. Control is affected by use of pilot operated valves, air pressure reducers and air valves. Pipework is of nylon with brass compression fittings.

The bolster and film feed slide were designed in the physics workshop, as were the film delivery and collecting magazines (see Fig. 1A and 1B).

Operation sequence

A film is collected from a vertical magazine by a sliding plate attached to a 15 cm stroke air cylinder. The thickness of the plate is such that only one film is collected. The film is fed along guides in a bolster into position under the press. At this point a valve operated by the feed cylinder initiates the press sequence and also returns the feed cylinder. The press returns by operation of a valve at the end of its stroke and also initiates the collection cylinder. Return of the collection cylinder by a valve at the end of its stroke restarts the sequence. The whole cycle is completed in approximately three seconds.

The delivery and collection magazines each hold one complete box of 150 films. The films are thus kept in sequential order which is necessary as they are processed twice. The numbering head is reversible to give two offset rows of four digits. In one mode the films are numbered sequentially, in the other the month and year of issue are added. This method of marking has been developed to meet the needs of certification by the Health and Safety Executive.

DISCUSSION

The most difficult problem to overcome was that of collecting the films. In the final design the films are allowed to fall into a shute and are positioned by gravity in front of the collecting ram to overcome the problem of dimensional variation in the wrapped film. Design of this shute is critical and early prototypes allowed the film to become trapped diagonally. Finally the film was fed with its long side parallel to the direction of movement. The numbering head was turned through ninety degrees to allow for this.

Variation in film marking can be obtained in three ways. The press is clamped onto a pillar and adjustment is obtained by raising or lowering. A suitable fine adjustment is incorporated for this purpose. The dwell can also be adjusted by varying the air pressure at a point in the circuit. We think this last factor plays an important part in achieving clear marking of the film. After the film has been processed, the digits can be read quite clearly even after heavy exposure to radiation. We also discovered that marking the reverse or yellow side of the film gives a very much improved result. Finally the air pressure to the whole system can be regulated.

Initial setting up is done empirically. Batches of six films are marked and processed until suitable results are obtained. The machine is then left set up.

1978, *British Journal of Radiology*, *51*, 1004–1010

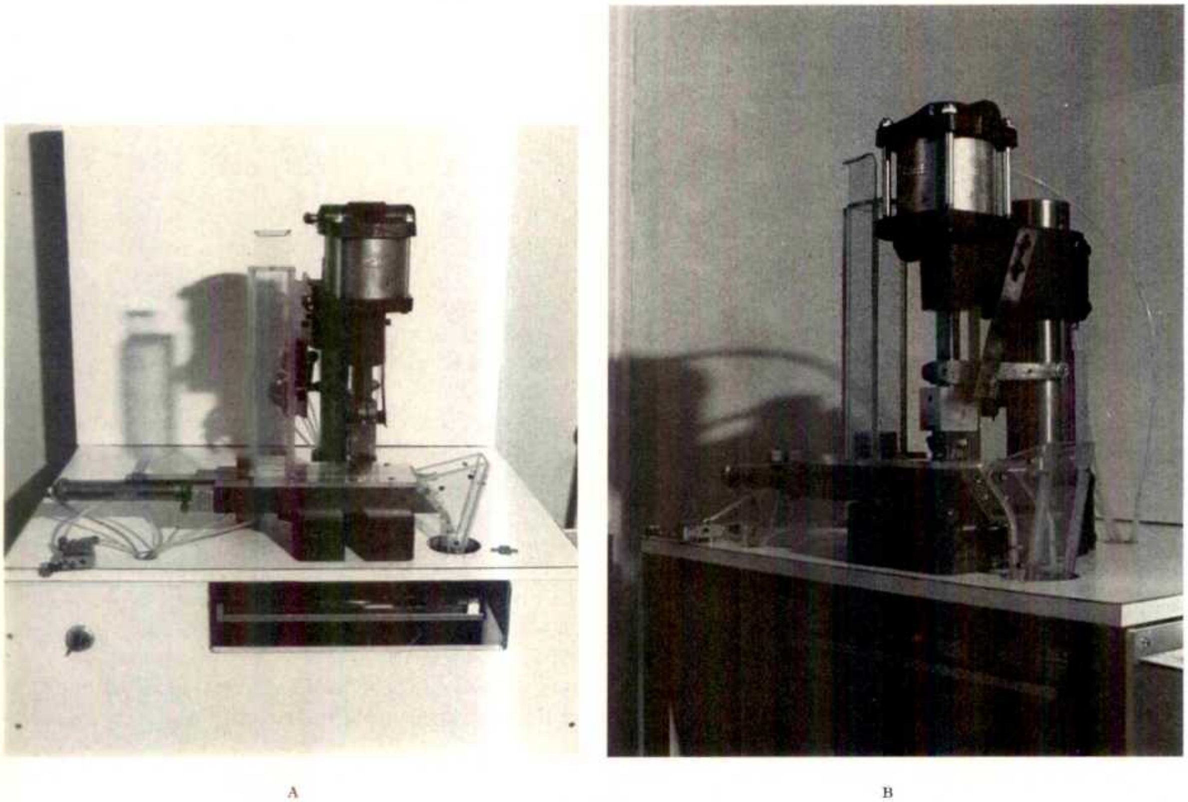


FIG. 1.

(A) A view of the press showing the film feed mechanism. (B) A view of the press showing the film collection shute with the collection magazine beneath.

The press has been evaluated and results are extremely good. Several batches of over one thousand films each have been marked and used satisfactorily by the Regional Protection Service. A batch of twelve hundred films can easily be completed in one day and, as the films are kept in numerical order, distribution to the various users is straightforward.

ACKNOWLEDGMENTS

We wish to thank Professor T. Shelley, Head of Physics, Southampton General Hospital, for his interest and encouragement, Mr. G. P. Donovan, formerly of Shraeder Pneumatics, for his kind initial help with the air circuit, and Hunts Fluid Power for the supply of additional components and advice.

Improvement of scanner performance by subtraction of Compton scattering using multiple energy windows

D. J. Waggett, Ph.D., D.I.C., A.R.C.S., and B. C. Wilson, B.Sc., Ph.D., M.Inst.P.*

Queensland Radium Institute, Royal Brisbane Hospital, Brisbane, Queensland, Australia

(Received November, 1977 and in revised form December, 1977)

In many radiological imaging situations photon scattering leads to degradation of image quality. Energy discrimination can substantially reduce the effects of scatter in radioisotope imaging. However, with low energy isotopes such as $^{99}\mathrm{Tc^m}$ the limited energy resolution of scintillators allows only imperfect discrimination against scattered photons.

With only a single energy channel available in a rectilinear scanner or gamma camera, a choice must be made between

---

*Now at Department of Radiology, Flinders Medical Centre, Adelaide, South Australia.

(a) the use of a high base-line energy, resulting in reduced sensitivity because of rejection of unscattered photons, or

(b) a low base-line setting to maximize the count-rate at the expense of image contrast and resolution.

Sanders *et al.* (1969), and Beck and Harper (1966), have examined the effects of energy selection to establish the optimum window setting for ^{99}Tc^{m} brain scanning. Rollo and Schulz (1971), and Sanders *et al.* (1972), extended this work to include an assessment of the detectability of lesions by observer-performance measurements. The former concluded that ". . . the energy-window base-line for ^{99}Tc^{m} is critical and should be set at 130 keV for optimum performance in detecting small focal lesions." Similarly, the latter found 133 keV to be optimal for imaging in the spatial frequency range above 0.1 cycles/cm.

As observed by Ehrhardt and Oberley (1972), however, the spectra obtained in clinical organ imaging vary considerably, even from point-to-point in a single view. Also large differences in the scatter/photopeak ratio between liver and brain scans have been observed by Hoffer *et al.* (1975). This variability makes it virtually impossible to determine *a priori* the optimum base-line setting in any scan. Furthermore, use of only a single energy window has the drawback that everything outside this window is ignored and thus information which could be obtained from the rest of the energy spectrum is wasted.

Various techniques for using information in the scattered part of the energy spectrum have been proposed. Ehrhardt and Oberley (1972), suggested using two windows for ^{99}Tc^{m} imaging: A (~70–95 keV) and B (> 125 keV). From the count rates within these windows the quantity $B-kA$ was then calculated and used to produce the image. Thus a fraction, k, of the counts within window A was taken as a measure of the scattered photon count within window B. This method assumes that k may be fixed throughout the scan and so no allowance is made for the point-to-point changes in the shape of the spectrum.

Bloch and Sanders (1973), adapted this idea by choosing the window settings such that $k=1$. Their method, as applied to ^{99}Tc^{m} scanning, was to measure and subtract the number of counts recorded in the energy interval of Compton scatter, 91–102 keV, from the counts recorded under the photopeak, 125–170 keV. These intervals were obtained by assuming that the Klein-Nishina equation for single Compton scattering adequately described the measured spectra. An improvement in image contrast was observed using a simulated liver phantom and a rectilinear scanner, with no appreciable loss in sensitivity for counting unscattered photons.

A system using three energy windows—the Variable Base-line Scanner—has been described by Oberley *et al.* (1972). In this the base-line of a third recording channel, C, of a rectilinear scanner was varied from point-to-point according to the ratio scatter events/photopeak events as measured in windows A (70–110 keV) and B (134–180 keV). This has the advantage of taking into account some of the changes in spectral shape across the scan. In regions where the scatter ratio, A/B, was high the base-line was moved up, and vice-versa. Significant improvements in image contrast were observed.

The disadvantage of the variable base-line system is that in areas with much scatter there is rejection of unscattered photons and hence a reduction in sensitivity.

In the present method, rather than varying the base-line of the recording channel, we have maintained a wide recording window for high sensitivity. Three other windows have then been used to determine the scatter component within the recording window, thus allowing this to be subtracted. On the rectilinear scanner used in developing the method, four channels were available and we have made use of all of them. The principle may be applied with less than four channels. However, in this case the determination of the energy spectrum shape and hence of the scatter component within the recording window will be less accurate.

The results presented here apply to ^{99}Tc^{m} imaging, using a Selo DS4 rectilinear scanner fitted with a 13.5 cm focal length converging collimator (FC9T). To establish appropriate window settings and to determine the relationships between the scatter component in the recording window and the count rates in the other three windows, energy spectra were measured using a ^{99}Tc^{m} flood source under a water bath of variable depth. Each spectrum was split into its photopeak and scattered components by an "edge-matching" technique to be described. The electronic module built to perform subtraction of scatter was based on these flood source results.

METHOD FOR SUBTRACTION OF SCATTER

Energy spectra with flood source

A ^{99}Tc^{m} flood source 35 cm × 35 cm square and 1 cm thick was located within the focal plane of the collimator and spectra were measured with depths, d, of 0.25, 1.25, 5.25 and 11.5 cm of water between the source and collimator. An additional spectrum at 18.5 cm depth was measured by moving the source to 6 cm beyond the focal plane. The width of the window was 2keV and the energy range measured was 25–200 keV.

For each spectrum the mean value between 175 and 200 keV was taken as the background and subtracted from the counts below 175 keV. Peak counts collected were typically about 4.10^4. The energy calibration of the scanner was determined using point sources of ^{129}I (39 keV), ^{133}Ba (80 keV), ^{57}Co (122 keV) and ^{131}I (284 keV) in air.

The spectrum of a ^{99}Tc^{m} point source in air was measured to determine the mean energy, $\bar{E}$, and the standard deviation, σ, of the Gaussian photopeak. The values were 140 keV and 11 keV respectively.

The photopeak and scattered components of each flood spectrum were separated as follows. It was assumed that above an energy, $E_{\max}$, to be determined at each depth the scattered component was negligible. Thus above $E_{\max}(d)$ the spectrum should be Gaussian with $\bar{E}=140$ keV and $\sigma=11$ keV. $E_{\max}$ (d) was determined by applying the constraints:

1. $E_{\max}$ as small as possible,
2. $He^{-(E-\bar{E})^2/2\sigma^2} \geqslant$ measured counts at E, for $E_{\max} < E \leqslant 175$ keV.

Thus, having calculated $E_{\max}$, the photopeak normalization, H, was then given by:

$H=$(measured counts at $E=E_{\max}$). $e^{(E_{\max}-\bar{E})^2/2\sigma}$

As would be expected, the "matching" energy $E_{\max}$ increased monotonically with depth from 144 ± 2 keV at $d=0.25$ cm to 158 ± 4 keV at $d=18.5$ cm. The error in $E_{\max}$ arises from the indeterminacy of constraint (2) due to the statistical fluctuations in the measured number of counts.

The considerable range in values of $E_{\max}$ confirms the need to take into account the variations in the shape of the scatter spectrum with depth, when applying scatter subtraction techniques.

The spectrum at 5.25 cm depth is shown in Fig. 1, together with its photopeak and scatter components. From the full set of such spectra, the relative count-rate contributions from scattered and unscattered photons within the selected energy windows were calculated as a function of depth.

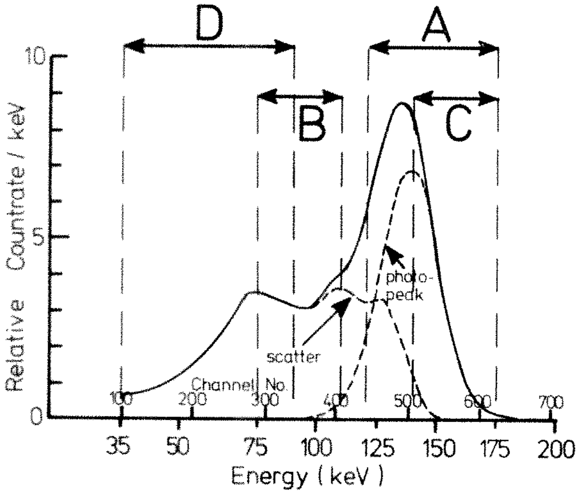


FIG. 1.

Energy spectrum at 5.25 cm depth showing the scatter and photopeak components and the energy windows A–D.

Window settings for scatter and photopeak

The settings chosen for the four Selo scanner windows were: window A: 120–175 keV; B: 75–110 keV; C: 140–175 keV; D: 35–90 keV. These are shown in Fig. 1.

The lower edge of the main recording window, A, corresponded to the cross-over point of the scatter and photopeak components at approximately 5 cm depth. Setting the base-line significantly lower than this would result in adding more scattered than unscattered photons at greater depths and would therefore only worsen the signal-to-noise ratio of the final image without significantly increasing the count-rate sensitivity. The count-rate within A thus consists of both scattered and photopeak events so that

$$\mathrm{CR_A}(d)=\mathrm{CR_A^{ph}}(d)+\mathrm{CR_A^{sc}}(d).$$

The second window, B, was chosen so that the ratio

$$f(d)=\mathrm{CR_A^{sc}}(d)/\mathrm{CR_B}(d)$$

was a sensitive but simple function of the flood source depth, d. The behaviour of this function is shown in Fig. 2.

Window C was set as high as possible, consistent with giving a reasonable count-rate, and so contains only a small contribution from scattered photons (1.6% at $d=0.25$ cm to 10.4% at $d=18.5$ cm). Window D was set so as to count only scattered photons. Thus the ratio

$$g(d)=\mathrm{CR_C}(d)/\mathrm{CR_D}(d)$$

is a good measure of the photopeak-to-scatter ratio at each depth. As seen in Fig. 2, g (d) decreases rapidly with depth up to about 10 cm and more slowly thereafter.

Thus, with this curve for g, the count-rate ratio $\mathrm{CR_C/CR_D}$ determines the depth of the source, d. This in turn determines the value of the function $f(d)$ and so the scatter component within A may be calculated from the count-rate within B using the relationship

$$\mathrm{CR_A}^{\mathrm{sc}} = f\,\mathrm{CR_B}.$$

In applying this to clinical scans we have assumed that d^*, as given by $g\,(d^*) = \mathrm{CR_C}/\mathrm{CR_D}$, is a good measure of the "effective" depth of the activity at the point scanned and thus that the functions f and g as determined from the spectra with the planar flood source apply to sources whose activity is distributed in depth. Calculations for extreme cases indicate that the values for $\mathrm{CR_A}^{\mathrm{sc}}/\mathrm{CR_A}$ obtained under this assumption should be accurate to within about 20%.

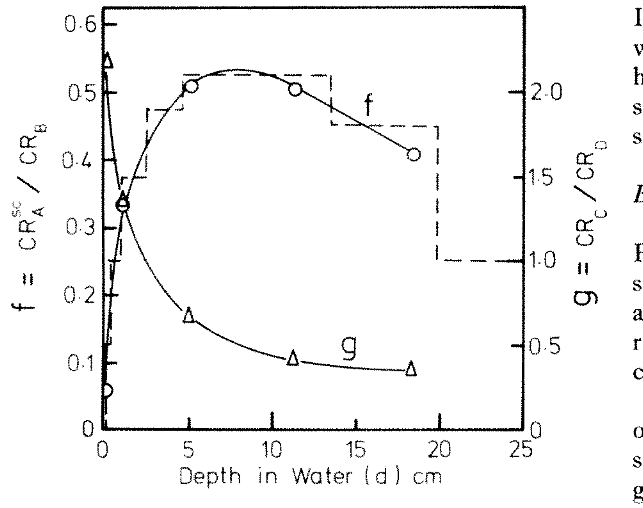


Fig. 2.

The scatter functions f and g as a function of the depth of the planar bath source. The broken line shows the eight-step electronic simulation of function f.

Thus we have, recorded count-rate at each scan point

$$\mathrm{CR_A}^{\mathrm{ph}} = \mathrm{CR_A} - f\,\mathrm{CR_B}$$

where f is determined from the measured value of g. In practice, g is not specifically calculated. Instead we have combined $f\,(g)$ into a single function which has been simulated electronically in eight discrete steps from the ratio $\mathrm{CR_C}/\mathrm{CR_D}$. The corresponding steps in $f\,(d)$ are shown in Fig. 2.

Electronics

A block diagram of the electronics is shown in Fig. 3*. The upper Selo detector head and associated pre-amplifier feeds the four pulse-height analysers. These four channels each feed a Selo ratemeter; two in a subtraction unit, the third in a colour tapper unit and the fourth in a photo-recorder.

An analogue division chip is used to divide the output of ratemeter C by that of D to produce a signal from which the value of the function $f\,(g)$ is generated stepwise, using eight comparators. These

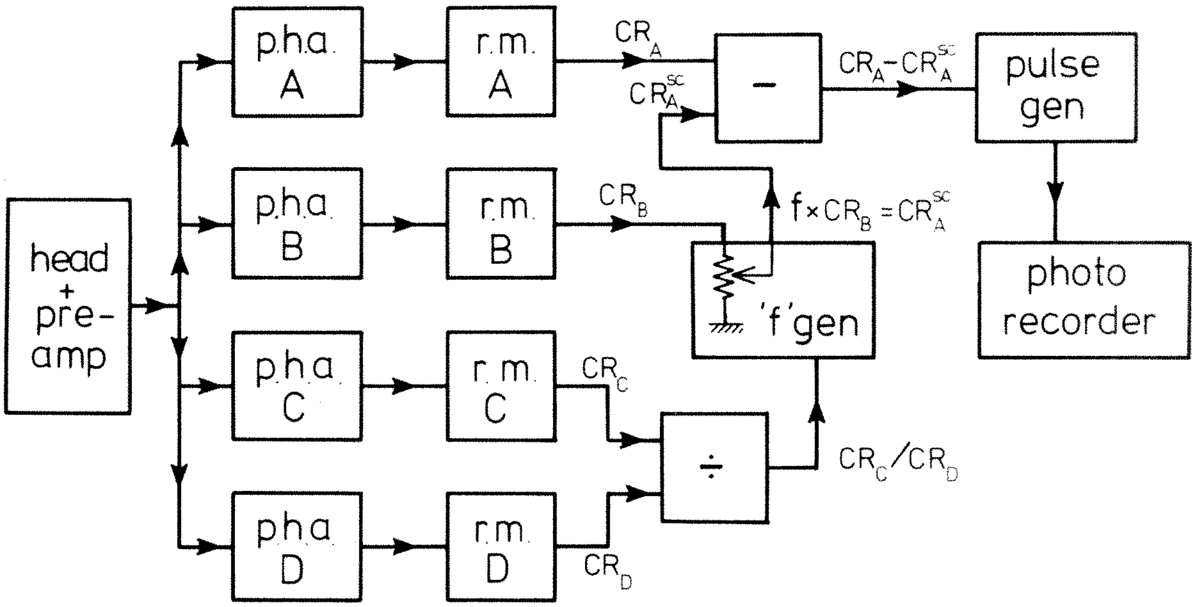


Fig. 3.

Block diagram of subtraction unit.

---

* Complete circuit diagrams are available on request from the authors.

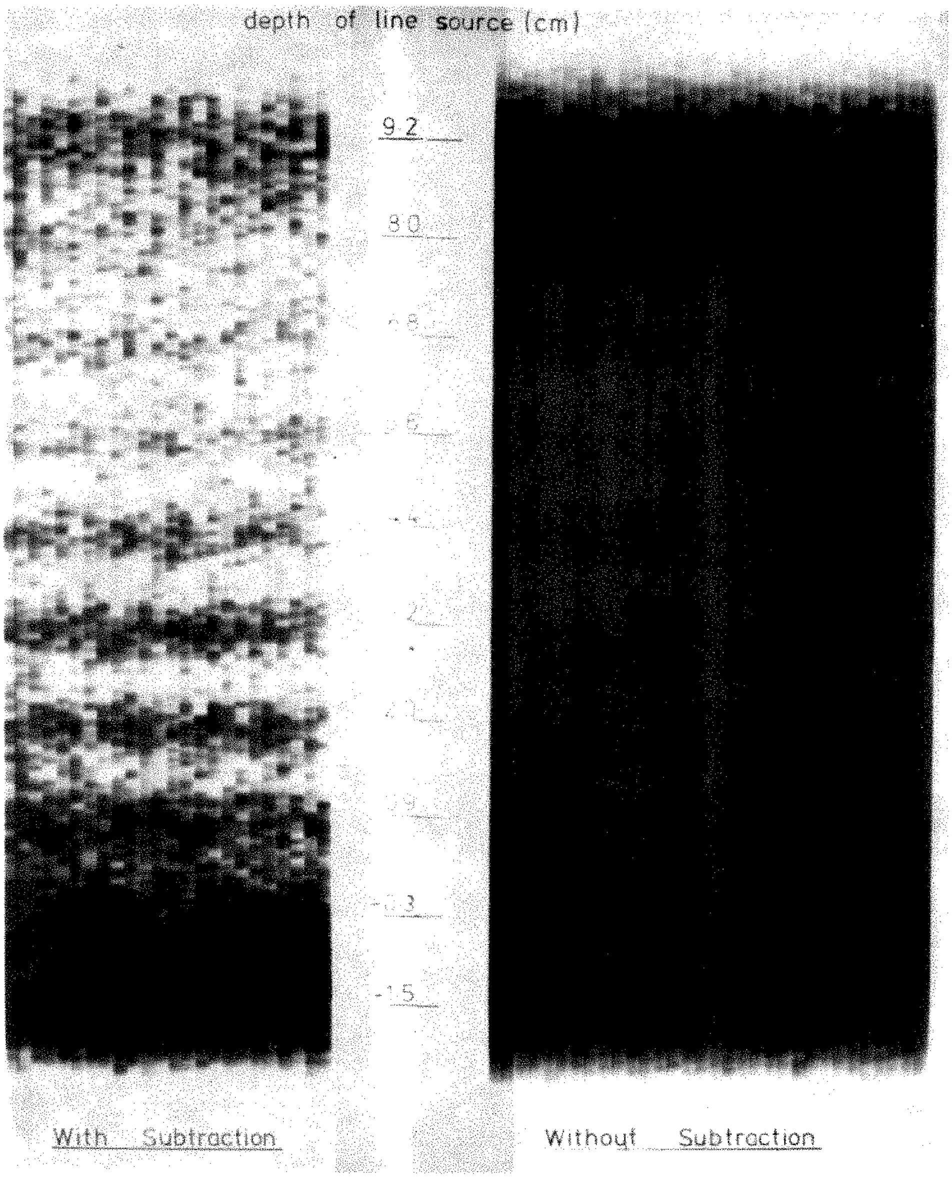


Fig. 4.

Images of the line source phantom with and without scatter subtraction. Both pictures have approximately the same maximum optical density. The depth of each line below the surface of the bath is indicated.

comparators drive transistor switches which modify the lower arm of the output attenuator of ratemeter B to give a transfer function of $f(g)$. The attenuated output of B, viz. CR_A^{sc}, is subtracted from the main channel A with a simple virtual-earth mixer to give the recording signal $CR_A^{ph} = CR_A - CR_A^{sc}$. This is converted into a pulse train suitable for driving the photo-recorder by using the voltage-controlled pulse generator within the Selo subtraction unit.

Results with Phantom

To test the system, scans were made of a phantom comprising ten $^{99}Tc^m$ line sources located on an inclined plane and placed in a bath uniformly filled with $^{99}Tc^m$. The plane was inclined at an angle of 24 deg to the horizontal and the bath was filled to a depth of 10.2 cm. The sources were 1 mm wide and lay horizontally at depths ranging from 1.5 cm above to 9.2 cm below the surface. The horizontal

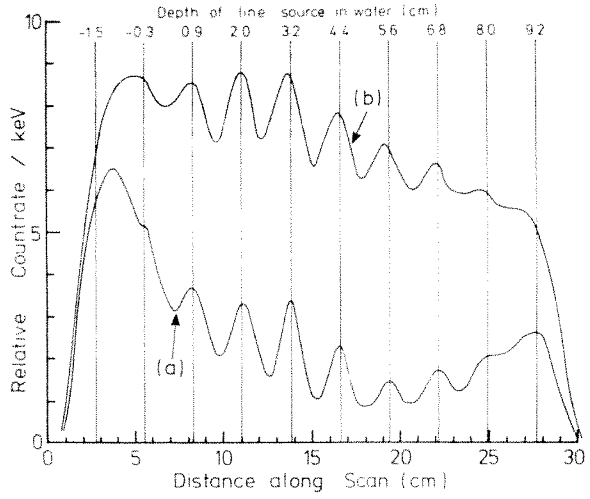


FIG. 5.

Densitometer traces of line source phantom. (A) with scatter subtraction as in Figure 4; (B) without scatter subtraction as in Figure 4.

separation of the lines was 2.75 cm. Scans were made with a detector looking downwards on the bath.

The sources each had a linear activity of 2.5 μCi cm^{-1} and the activity of the bath was chosen to give a count-rate contribution approximately equal to that of a single line. This corresponded to a planar activity of about 2 μCi cm^{-2}. The focal plane of the collimator was set 4 cm below the surface.

Figure 4 shows a scatter-subtracted scan of this phantom and also a scan performed without subtraction (channel B disconnected). The exposures were set so as to give approximately the same maximum optical density on both films.

Densitometer traces of these films, converted from optical density to relative count-rate, are shown in Fig. 5. The densitometer aperture was 0.5 mm wide and in each trace the count-rate has been averaged over a 6.4 cm length of the line sources to reduce the noise level.

It is difficult to assess the improvement in image quality from Fig. 4. However, as may be seen from Fig. 5, the quantitative effect of scatter subtraction is significant. For example, defining the image modulation as

$$M = \frac{\mathrm{CR}_{\mathrm{peak}} - \mathrm{CR}_{\mathrm{trough}}}{\mathrm{CR}_{\mathrm{peak}} + \mathrm{CR}_{\mathrm{trough}}}$$

then the ratio $M_{\mathrm{subtracted}}/M_{\mathrm{unsubtracted}}$ takes values between 3 and 4 for lines lying below the surface, as given by curves (A) and (B).

Also, the full-width at $\frac{1}{2}$(peak+trough) has been reduced from about 16 mm to 12 mm near the focal plane. This improvement must be judged bearing in mind the loss of count-rate arising from subtraction of scatter.

The ratio of count-rate with and without scatter subtraction for the line phantom was 0.65, averaged over the scan. However, there is still a 55% increase in photopeak count-rate compared with that obtained with the usual $\pm 10\%$ window width.

CONCLUSIONS

We have shown that it is possible to use multiple energy windows to achieve scatter subtraction in radioisotope scans and thereby improve image contrast and resolution, particularly at depth. While it is true that some improvement in contrast could be gained by simple contrast enhancement, this would not lead to improved resolution. The improvement in image quality which we have observed has been achieved without significant loss of sensitivity.

On the debit side we note that any subtraction technique reduces the signal-to-noise ratio of the image. As pointed out by Ehrhardt *et al.* (1974), the signal-to-noise can be maximized if the photons at each energy are made to contribute to the image with weighting factors which may be positive or negative. The idea of using the full energy spectrum in this way is attractive and would probably give better results than the method reported here.

However, we consider a major advantage of the present technique is that it can be implemented using existing rectilinear scanner channels at very low cost, both in terms of hardware and effort. Furthermore, the principle of scatter subtraction with allowance for depth variations in the activity can be applied to other instruments with only three, or at a pinch two, energy windows.

We are currently evaluating the role of the above system in the clinical situation. The most promising area of application is in imaging deep-lying structures where degradation due to Compton scattering is greatest. Results to date are encouraging, indicating that worthwhile clinical benefit can be gained. We expect to present the clinical results in a future paper.

Although demonstrated for a particular rectilinear scanner, the technique is applicable to radionuclide imaging in general and work is in progress to use the method with an Anger camera.

REFERENCES

BECK, R. N., and HARPER, P. V., 1966. Criteria for evaluating radioisotope imaging systems. *Fundamental Problems in Scanning* (Charles C. Thomas, Springfield).

BLOCH, P., and SANDERS, T., 1973. Reduction of the effects of scattered radiation on a sodium iodide imaging system. *Journal of Nuclear Medicine*, *14*, 67–72.

EHRHARDT, J. C., and OBERLEY, L. W., 1972. Effects of spectral changes on scanning. *Radiology*, *104*, 207–208.

EHRHARDT, J. C., OBERLEY, L. W., and LENSINK, S. C., 1974. Effect of a scattering medium on gamma-ray imaging. *Journal of Nuclear Medicine*, *15*, 943–948.

HOFFER, P., BECK, R., STARK, V., and BEKERMAN, C., 1975. Measurement of scatter fraction in liver and brain scans performed with a gamma camera. *Journal of Nuclear Medicine*, *16*, 535.

OBERLEY, L. W., EHRHARDT, J. C., and LENSINK, S. C., 1972. The variable base-line scanner. *Physics in Medicine and Biology*, *17*, 630–637.

ROLLO, F. D., and SCHULZ, A. G., 1971. Effect of pulse-height selection on lesion detection performance. *Journal of Nuclear Medicine*, *12*, 690–696.

SANDERS, T. P., COHEN, T. D., and KUHL, D. E., 1969. Optimising the window setting of an Anger camera for ^{99}Tc^{m}. *Journal of Nucelar Medicine*, *10*, 369.

SANDERS, T. P., SANDERS, T. D., and KUHL, D. E., 1972. Optimising the window of an Anger camera for ^{99}Tc^{m}. *Journal of Nuclear Medicine*, *12*, 703–706.

Book review

A Radiographic Index—6th Edition. By M. Goldman and D. Cope, pp. iv+98, 1978 (John Wright & Sons Ltd, Bristol), £2·50.

This most valuable pocket book sized radiographic index makes its sixth appearance on the radiographic stage, three years after the fifth edition and 17 years after its debut. Designed for student radiographers and radiographers, it has rightly gained world wide popularity. The first two thirds of the book comprise the radiographic index which includes a brief synopsis of the radiographic and radiological investigation techniques for all parts of the body, presented in alphabetical order. The last third of the book consists of seven appendices dealing with the contrast media, medical terms, abbreviations, exposure tables, named views of the skull, some normal blood values and a new appendix dealing briefly with the ten day rule. All sections have been updated and brief notes on the newer techniques including CT scanning have been incorporated.

The preparation of any synopsis involves difficult decisions regarding what to include and what to discard. This selection of material for this volume has on the whole been successful, although doubtless the experienced reader will inevitably disagree with the choice in one or two places. For example, in the entry on normal urea the opinion is expressed that normal dose urography is unlikely to be effective if blood urea is much above 10 mmol/1 per litre, which begs the question of what represents a normal dose, but no mention is made of the importance of avoiding preliminary fluid restrictions in patients with azotaemia.

In bringing this edition up-to-date, the authors have successfully maintained the previous high standard of this book. It will serve as an admirable introduction to the subject for the student radiographer and will remain an admirable *aide memoire* when the student has become more experienced. Every new student radiographer should be urged to purchase a copy and keep it constantly available in the pocket for which it was designed.

JOHN QUICK

1978, *British Journal of Radiology*, *51*, 1011–1012 DECEMBER 1978

Case reports

Obstructive jaundice caused by cavernous transformation of the portal vein

By H. C. Meredith, M.B., B.S., M.R.A.C.R., I. Vujic, M.D., S. I. Schabel, M.D., and P. H. O'Brien, M.D.

Department of Radiology and Department of Surgery, Medical University of South Carolina, Charleston, South Carolina 29403, USA

(*Received January, 1978 and in revised form August, 1978*)

Extrahepatic portal obstruction developing in the neonatal period usually presents with manifestations of portal hypertension. Obstructive jaundice has not previously been described as a complication of this condition.

CASE REPORT

A 22 year-old white male presented with jaundice, decreased appetite and tiredness for six months. He was known to have portal hypertension which followed neonatal omphalitis and portal vein thrombosis. At age four, splenectomy and lieno-renal shunt was done because of bleeding from oesophageal varices. Two further, self-limiting episodes of gastrointestinal bleeding occurred in his teens.

He was normally developed and showed no other abnormalities apart from jaundice. Total bilirubin was 10.4 mgm% with a direct fraction of 7.2 mgm%. Alkaline phosphatase was elevated to 344 K.A. units, but liver function tests were otherwise normal. Liver biopsy was unsuccessful, but was complicated by puncture of the gall-bladder with haemorrhage into it, necessitating laparotomy. The wall of the gall-bladder was found to contain varices, one of which was oversewn to control bleeding and a cholecystostomy tube was inserted. Serum bilirubin fell to 3.6 mgm%. Angiography showed oesophageal varices, non-patent lieno-renal shunt, thrombosis of the proximal superior mesenteric vein and cavernous transformation of the portal vein, with varices in the region of the common bile duct (Fig. 1). The patient was re-explored because tube cholecystography revealed marked narrowing and displacement of the distal common bile duct. Varices were found in the region of the common bile duct

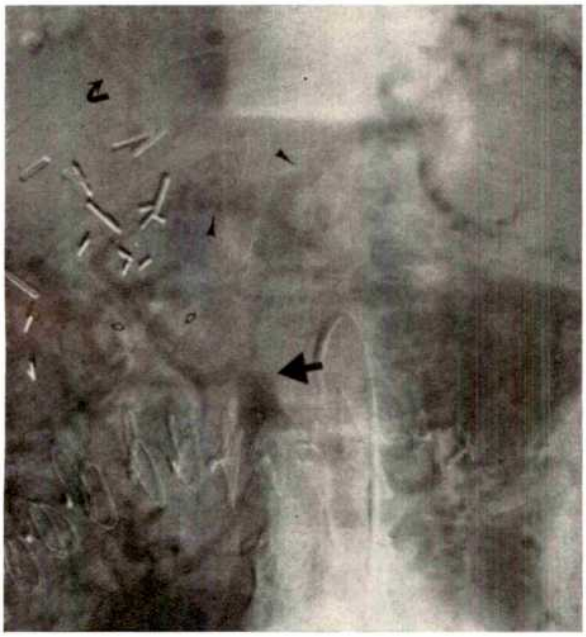


FIG. 1.

Subtraction film of venous phase of superior mesenteric angiogram. Large arrow—occlusion of proximal superior mesenteric vein. Closed arrow—peri-portal varices in the region of the common bile duct. Arrow heads—hepatofugal shunting into coronary and oesophageal veins. Curved arrow—filling of intrahepatic portal venous radicles, via peri-portal collaterals.

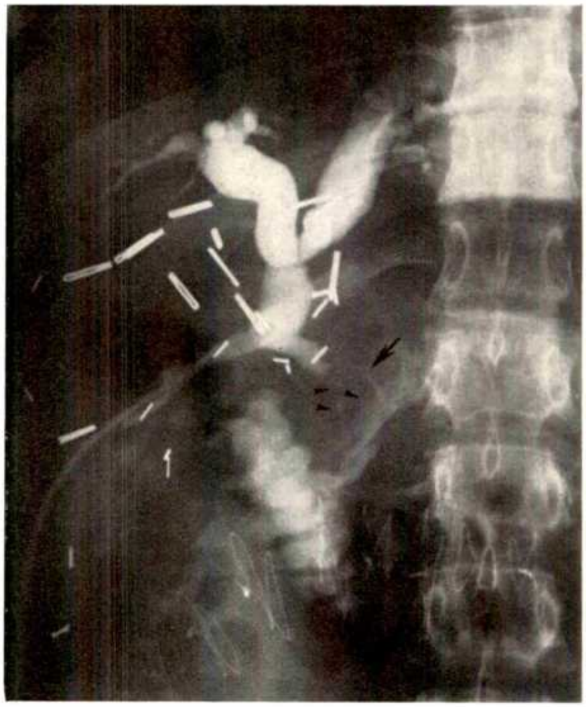


FIG. 2.

T-tube cholangiogram showing displacement and narrowing of the distal common bile duct. Large arrows—peri-portal varices. Small arrow heads—linear streaks of calcification in region of varices.

1978, *British Journal of Radiology*, *51*, 1012–1014

and also in the gall-bladder wall, with no other lesion. Portal pressure was 45 mg Hg. The gall-bladder was judged unsuitable for cholecystojejunostomy and was removed. A T-tube was inserted into the common bile duct and he recovered well, apart from an episode of cholangitis, which responded to antibiotics. Serum bilirubin fell to normal but a T-tube cholangiogram showed persistent narrowing and displacement of the common bile duct by peri-portal varices, which also showed fine linear calcifications (Fig. 2). Mesocaval shunt and choledochoenterostomy are under consideration.

DISCUSSION

In the neonate, the umbilical vein forms a potential pathway for the spread of phlebitis and thrombosis from the umbilicus to the portal vein. Described causes of this complication include idiopathic, umbilical sepsis, exchange transfusions, laevulose infusions, dehydration and congenital anomalies of the portal vein (Wilson *et al.*, 1969; Rosch and Dotter, 1971). Hepatopedal flow from splenic and mesenteric veins to the liver is maintained by the development of collateral venous channels in the lesser omentum, so-called cavernous transformation of the portal vein (Fig. 1). These collateral vessels are inadequate to prevent portal hypertension (Rosch and Dotter, 1971).

The most common presentation of extra-hepatic portal obstruction is bleeding from oesophageal varices. Salicylates have been thought to be a contributing factor in some patients (Wilson *et al.*, 1969). Splenomegaly, hypersplenism, anaemia, chronic diarrhoea and ascites have also been described (Wilson *et al.*, 1969; Rosch and Dotter, 1971; Laws *et al.*, 1959). Obstructive jaundice has not previously been described due to periportal collateral vein formation. In our patient, jaundice was caused by compression of the common bile duct by periportal varices in the lesser omentum, which were seen at surgery and radiographically (Figs. 1 and 2). Calcification in the portal venuos system is uncommon and has been associated in all cases with portal vein thrombosis usually complicating cirrhosis (Blendis *et al.*, 1968). The calcification has occurred in the walls of the portal venous system and within thrombi. The linear streaks of calcification seen in our patient (Fig. 2), is an unusual finding and is probably present in the walls of the varices.

REFERENCES

BLENDIS, L. M., LAWS, J. W., WILLIAMS, R., and THOMSON, W. B., 1968. Calcified collateral veins and gross dilatation of the azygous vein in cirrhosis. *British Journal of Radiology*, *41*, 909–912.

LAWS, J. W., LEIGH, R., and STEINER, R. E., 1959. Extrahepatic portal vein obstruction. *British Journal of Surgery*, *32*, 774–790.

ROSCH, J. and DOTTER, C. T., 1971. Extrahepatic portal obstruction in childhood and its angiographic diagnosis. *American Journal of Roentgenology*, 112, 143–149.

WILSON, K. W., ROBINSON, D. C., and HACKING, P. M., 1969. Portal hypertension in childhood. *British Journal of Surgery*, *56*, 13–22.

Tuberculosis of the breast

By A. Ward, F.R.C.S., F.R.A.C.S., S. Field, M.A., F.R.C.R., and R. E. C. Collins, F.R.C.S.

Kent and Canterbury Hospital, Canterbury CT1 3NG

(*Received March, 1978*)

Tuberculosis of the breast is rare in western countries (Haagensen, 1971; Raw, 1924), and is unusual even in countries where other forms of tuberculosis are common (Mukerjee *et al.*, 1974). It usually presents as a mass or abscess in the breast and clinically may be mistaken for a carcinoma. Indeed carcinoma and tuberculosis may co-exist in the same breast (Miller *et al.*, 1971; Grausman and Goldman, 1945). We wish to present a case in which the diagnosis of tuberculosis of the breast was made radiologically prior to surgery.

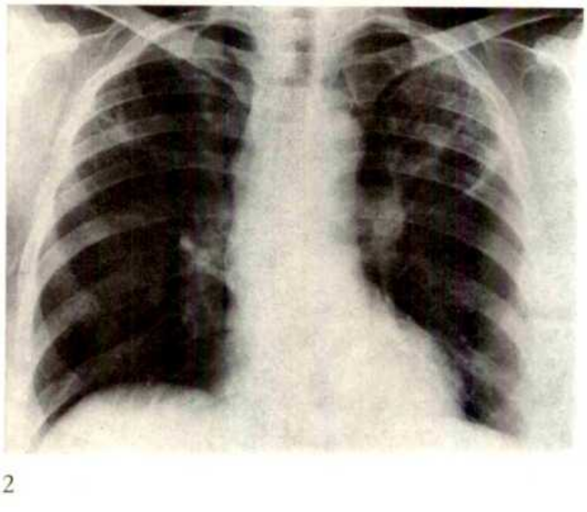


FIG. 1.

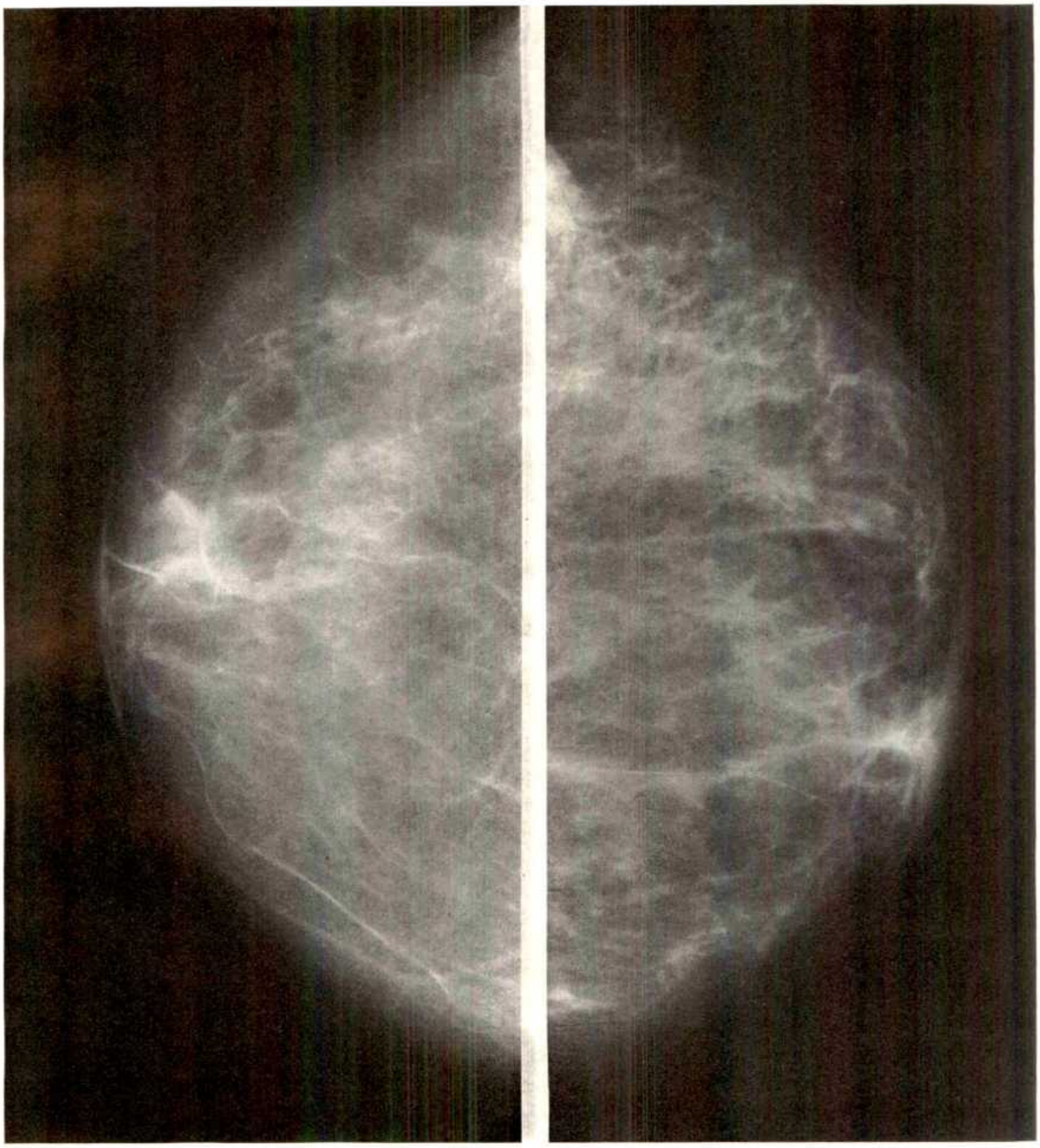
Postero-anterior chest radiograph showing bilateral upper zone consolidation and left hilar lymph node enlargement.

CASE REPORT

A 60-year-old caucasian woman presented with a painless mass in her left breast. On examination there was a very firm, non-tender, 9 cm diameter mass in the upper outer quadrant of the breast. There was no axillary lymphadenopathy. A routine pre-operative chest radiograph demonstrated consolidation in both upper lobes, more marked on the left, and enlarged left hilar lymph nodes (Fig. 1). Mammography (Figs. 2A and B) demonstrated marked skin thickening laterally and thickened, distorted trabeculae with loss of normal architecture throughout the breast. Surgical exploration of the mass produced pus containing tubercle bacilli. Subsequent sputum specimens were also positive for tubercle bacilli.

DISCUSSION

There have been very few reports of the use of mammography in the diagnosis of tuberculosis of the



A FIG. 2. B

(A) Mammogram of right breast. Cranio-caudal view. Normal appearances.

(B) Mammogram of left breast. Cranio-caudal view showing skin thickening laterally and thickened, distorted, trabeculae.

breast. Features previously noted have been non-specific dense mass lesions of variable size and shape but with no skin thickening (Gottschalk *et al.*, 1976), and dense oval areas with irregular contours suggesting malignancy (Tabar *et al.*, 1976).

Mammographic changes similar to those described in our case have been reported (Leborgne, 1953) and are suggestive of a diffuse inflammatory process or an infiltrating carcinoma. There was no clinical evidence of chest disease in this patient but the routine pre-operative chest radiograph and subsequent tomography were highly suggestive of active tuberculosis. The appearances on the chest radiograph and mammographs taken together made it possible to make a presumptive diagnosis of tuberculosis of the breast pre-operatively.

CONCLUSION

The mammographic features of tuberculosis of the breast are non-specific but it is suggested that there should be a greater awareness of the disease especially as the incidence of tuberculosis may be increasing (Prowse and Cavanagh, 1976) and there were 2453 cases of non-respiratory tuberculosis in England and Wales in 1973 (Registrar General's figures).

REFERENCES

GOTTSCHALK, F. A. B., DECKER, G. A. G., and SCHMAMAN, A., 1976. Tuberculosis of the breast. *South African Journal of Surgery*, *14*, 19–22.

GRAUSMAN, R. L., and GOLDMAN, M. L., 1945. Tuberculosis of the breast. Report of nine cases including two cases of co-existing carcinoma and tuberculosis. *American Journal of Surgery*, *67*, 48–56.

HAAGENSEN, C. D., 1971. In *Diseases of the Breast*, 2nd edn. (Saunders, Philadelphia).

LEBORGNE, R. A., 1953. In *The Breast in Roentgen Diagnosis*, pp. 177–183 (Impresora Uraguaya S.A., Montevideo, Constable and Co. Ltd., London).

MILLER, R. E., SALOMAN, P. F., and WEST, J. P., 1971. The co-existence of carcinoma and tuberculosis of the breast and axillary lymph nodes. *American Journal of Surgery*, *121*, 338–340.

MUKERJEE, P., GEORGE, M., MAHESHWARI, H. B., and RAO, C. P., 1974. Tuberculosis of the breast. *Journal of the India Medical Association*, *62*, 410–42.

PROWSE, K., and CAVANAGH, P., 1976. Tuberculosis in the Potteries. 1971–74. *Lancet*, *2*, 357–359.

RAW, N., 1924. Tuberculosis of the breast. *British Medical Journal*, *1*, 657–658.

TABAR, L., KETT, K., and NEMETH, A., 1976. Tuberculosis of the breast. *Radiology*, *118*, 587–589.

Spasm of the superior mesenteric artery complicating methysergide maleate therapy

By P. Lowe, M.B., Ch.B., B.Sc., F.R.C.R.,* A. Hoiseth, M.D., and T. Nordshus, M.D.

Department of Radiology, Ulleval Hospital, Oslo, Norway

(*Received February, 1978*)

Methysergide maleate has been used since the early sixties as prophylactic therapy in the management of migraine and other vascular headaches. Many mild side-effects have been reported such as nausea, dizziness and rashes, and also some major complications including retroperitoneal fibrosis, cardio-pulmonary changes, limb ischaemia, abdominal angina and bowel infarction (Graham *et al.*, 1966; Bana *et al.*, 1974; Rackley *et al.*, 1966).

The major complications of treatment are the result of vascular spasm and fibrosis (Graham *et al.*, 1966) but the mode of action of methysergide in producing these changes is not known. The spasm resolves within seven days of discontinuing the drug and even extensive fibrosis can subsequently show some regression (Ureles and Rob, 1963).

Vascular spasm has been reported in all the major limb arteries, the carotid, coronary and gastro-intestinal arteries and the aorta (Graham, 1967). However, the diagnosis of spasm has in most cases been made on the clinical findings alone, and confirmatory arteriography has been carried out in only a small number of patients, mainly those with peripheral ischaemia (Raw and Gaylis, 1976; Rackley *et al.*, 1966; Dalinka and McGee, 1970). A case is therefore reported of a patient on treatment with methysergide maleate who developed spasm of the superior mesenteric artery and was investigated by angiography both before and after discontinuation of the drug.

CASE HISTORY

A 38-year-old woman was admitted as an emergency (in April, 1977), because of severe abdominal pain of 48 hours duration. Since the age of 14 years she had suffered from migraine, with repeated attacks of severe right-sided headaches and vomiting usually at the time of menstruation. This had been frequently treated with ergotamine tartrate orally (Cafergot) but in 1971 this treatment was stopped, and she commenced using ergotamine tartrate suppositories (Anerven). She used up to two suppositories three times weekly.

---

*Present address: Department of Radiology, Shrewsbury Hospital, Shrewsbury.

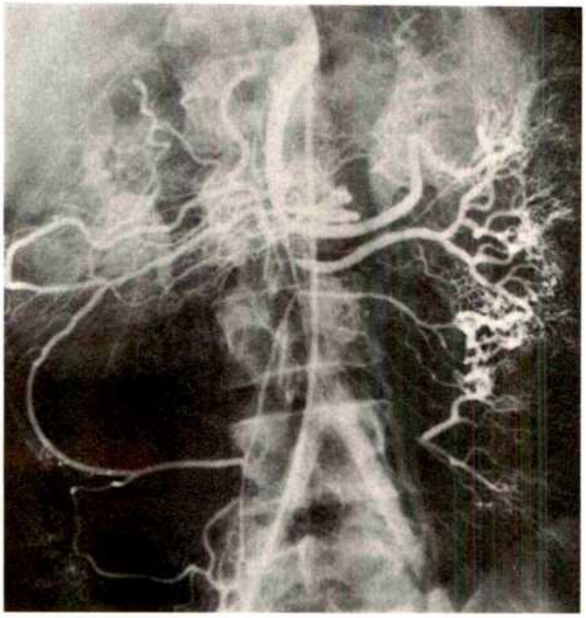


FIG. 1.
Selective superior mesenteric arteriogram in May 1977 showing multiple areas of spasm.

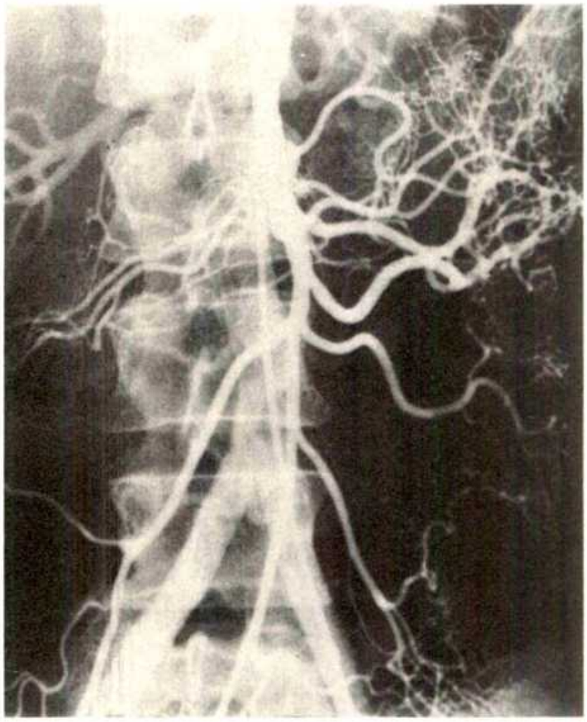


FIG. 2.
Repeat superior mesenteric arteriogram in October 1977 showing normal appearances.

In September 1976 she stopped using the suppositories because they were no longer controlling her migraine and started taking methysergide maleate (Deseril) orally, up to two 3 mg tablets twice daily for periods of up to one month and then with three to four weeks between periods of usage.

She had first noticed the abdominal pains in 1970. They occurred after food and mainly on the right side of the abdomen. They were colicky in nature and had slowly increased in severity up to the time of her acute admission.

An intravenous cholangiogram in 1970, a barium meal, urography and plain films of the hips and pelvis in 1975 were all normal. An ECG was also normal.

On admission she had a regular pulse (76/minute), a blood pressure of 135/70 and normal peripheral pulses. There was an arterial bruit in the epigastrium with some radiation towards the left lumbar region. Haemoglobin was 6.8 mmol/l, white blood count 5500 mm^3, urea 5 mmol/l and amylase 257 units. Plain abdominal films and a small bowel study were normal.

Because the patient's symptoms suggested abdominal angina, selective coeliac, superior and inferior mesenteric arteriography was performed. There was a long tapering stenosis of the main superior mesenteric artery with complete occlusion just distal to the origin of the ileo-colic artery. Some of the jejunal arteries, the ileo-colic artery and the few ileal branches which were demonstrated were all markedly narrowed. The walls of the narrowed vessels were smooth. Many of the small ileal vessels could not be filled. The ileo-colic loop was mainly filled through the right colic artery (Fig. 1). The coeliac and inferior mesenteric arteries were normal. An arch aortogram was normal.

As a result of the angiographic findings, the methysergide maleate was discontinued and the headaches treated by simple analgesics. Glucagon 1 mg i.m. was given three times daily before meals to increase splanchnic blood flow. Six days after stopping the methysergide the arterial bruit had disappeared. The abdominal pains subsided, although the patient still complained of vague pains two to three months later. However, there was no recurrence of the previous abdominal angina and six months later the patient was free from pain and a repeat arteriogram demonstrated a normal superior mesenteric artery (Fig. 2).

DISCUSSION

The patient's abdominal pains started before commencement of treatment with methysergide. However, she had previously been taking ergotamine derivatives and it is known that patients who are hypersensitive to this drug can also develop abdominal pain, severe enough to merit laparotomy (Rømer and Nielsen, 1973), peripheral ischaemia and even gangrene (Kempczinski *et al.*, 1976; Bagby and Cooper, 1972). These complications result from arterial spasm and thrombosis but the spasm subsides within a week of stopping treatment (Hirsch and Eger, 1972).

Thus although the patient's original symptoms may have been produced by ergotamine, the angiographic findings, the arterial bruit and the severe abdominal pain at the time of the acute admission in 1977 can only be ascribed to the methysergide maleate and the disappearance of these symptoms and signs after stopping the drug provides further confirmation.

1978, *British Journal of Radiology*, *51*, 1016–1018

The smooth stenoses and occlusions of the vessels are similar in appearance to those described in the major limb vessels as a complication of methysergide therapy by Raw and Gaylis (1976), Rackley *et al.* (1966) and Dalinka and McGee (1970).

However, apart from our case only one other with arteriographically demonstrable changes in the superior mesenteric artery attributable to methysergide therapy appears to have been described (Buenger and Hunter, 1966). In this patient there were multiple smooth stenoses of the proximal branches of the superior mesenteric artery with some beaded stenoses more peripherally. No collateral supply from the coeliac artery or inferior mesenteric artery was found and the authors suggested this was probably because there was involvement of vessels distal to the normal sites of collateral flow. In our case a collateral supply to the ileum and ileo-colic region was present only through the proximal jejunal arteries and the right colic artery and these enlarged vessels returned to normal size (Fig. 2) after discontinuing the drug. In both patients the arteriographic abnormalities, arterial bruit and clinical symptoms resolved after withdrawal of methysergide treatment. Presumably if treatment is continued adventitial fibrosis can develop and ultimately infarction of small bowel, as in the case reported by Regan and Poletti (1968).

The arteriographic findings of long and short widespread tapering stenoses with fine smooth-walled vessels are similar to those found in ergotamine hypersensitivity. However, the patient's clinical history would indicate which particular drug is involved. Arteriosclerotic changes rarely involve only the superior mesenteric artery and are usually distributed close to its origin. Fibro-muscular hyperplasia may occasionally involve the gastro-intestinal vessels, but the changes are of short localized stenoses with or without associated dilatations ("string of beads") and should give no difficulty in the differential diagnosis.

REFERENCES

Bagby, R. J., and Cooper, R. D., 1972. Angiography in ergotism. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 116*, 179–186.

Bana, D. S., MacNeal, P. S., Le Compte, P., Shah, Y., and Graham, J. R., 1974. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *American Heart Journal, 88*, 640–655.

Buenger, R. E., and Hunter, J. A., 1966. Reversible mesenteric artery stenoses due to methysergide maleate. *Journal of the American Medical Association, 198*, 558–560.

Dalinka, M. K., and McGee, J. W., 1970. The variable manifestations of sclerosing fibrosis. *Journal of the Canadian Association of Radiologists, 21*, 280–286.

Graham, J. R., 1967. Current therapeutics—methysergide. *The Practitioner, 198*, 302–311.

Graham, J. R., Guby, H. I., Le Compte, P. M., and Safowsky, N. L., 1966. Fibrotic disorders associated with methysergide therapy for headaches. *New England Journal of Medicine, 274*, 359–368.

Hirsch, M., and Eger, M., 1972. Angiography in the diagnosis of ergotism. *Radiology, 103*, 89–90.

Kempczinski, R. F., Buckley, C. J., and Darling, R. C., 1976. Vascular insufficiency secondary to ergotism. *Surgery, 79*, 597–600.

Rackley, C., Mengel, C. E., Pomerantz, M., and McIntosh, H. D., 1966. Vascular complications with use of methysergide. *Archives of Internal Medicine, 117*, 256–269.

Raw, K., and Gaylis, H., 1976. Acute arterial spasm of the lower extremities after methysergide therapy. *South African Medical Journal, 50*, 1999–2001.

Regan, J. F., and Poletti, B. J., 1968. Vascular adventitial fibrosis in a patient taking methysergide maleate. *Journal of the American Medical Association, 203*, 1069–1071.

Rømer, A. F., and Nielsen, J. L., 1973. Ergotamin Forgift differential diagnose ved Akut Abdomen. *Ugeskrift for Laeger, 135*, 1695–1697.

Ureles, A. L., and Rob, C., 1963. Acute ischaemia of a limb complicating methysergide maleate therapy. *Journal of the American Medical Association, 183*, 1041–1042.

Grey-scale ultrasound demonstration of ureterocele and hydroureter

By V. L. B. Nikapota, M.B., B.S., D.M.R.(D.), F.R.C.R., and M. I. Wray, M. B., B.S., D.M.R.(D.)

Department of Radiodiagnosis, Barnet General Hospital, Wellhouse Lane, Barnet, Herts.

(Received March, 1978)

Congenital stenosis of a ureteric orifice causes cystic enlargement of the intramural portion of the ureter. This is termed ureterocele (Bailey and Love, 1959).

We have been unable to find any previous report of the demonstration of ureterocele by grey-scale ultrasound and record here the findings in a case where ultrasound was instrumental in establishing the diagnosis.

Case Report

During investigation for prostatism on a 75-year-old man, routine intravenous urography revealed a right sided hydronephrosis and a collection of contrast in the region of the lower end of the right ureter (Fig. 1). A possible lucent filling defect was identified within this collection of contrast. Concentration of the contrast medium in this region and in the bladder was poor owing to dilution by retained urine. It was considered likely that a right ureterocele was present and grey-scale ultrasound examination was performed to confirm the diagnosis.

The patient was examined in a supine position using a Nuclear Enterprises Diasonograph NE 4200 with grey-scale display and 2.5 MHz 19 mm transducer.

The ultrasound scan (Fig. 2) clearly outlined a ureterocele and the lower portion of the dilated ureter was also shown. Multiple echogenic structures were noted within the ureterocele and probably confirm the radiological impression of calculi here. In addition, a posterior bladder diverticulum containing a calculus was also noted (Fig. 2) The prostate was confirmed to be enlarged.

These findings were not confirmed at surgery since the patient died of unrelated disease shortly after these investigations.

DISCUSSION

Demonstration of the ureters by ultrasound is almost always difficult in the supine position due to overlying gas-containing loops of bowel which interfere with adequate transmission of the ultrasound beam. In the prone position the examination is also impossible owing to interposition of the vertebral transverse processes, sacrum and ileum.

Our patient had a markedly scaphoid abdomen with no gas-containing bowel over his sacral region and ultrasound examination was therefore feasible. Considerable distension of the urinary bladder may

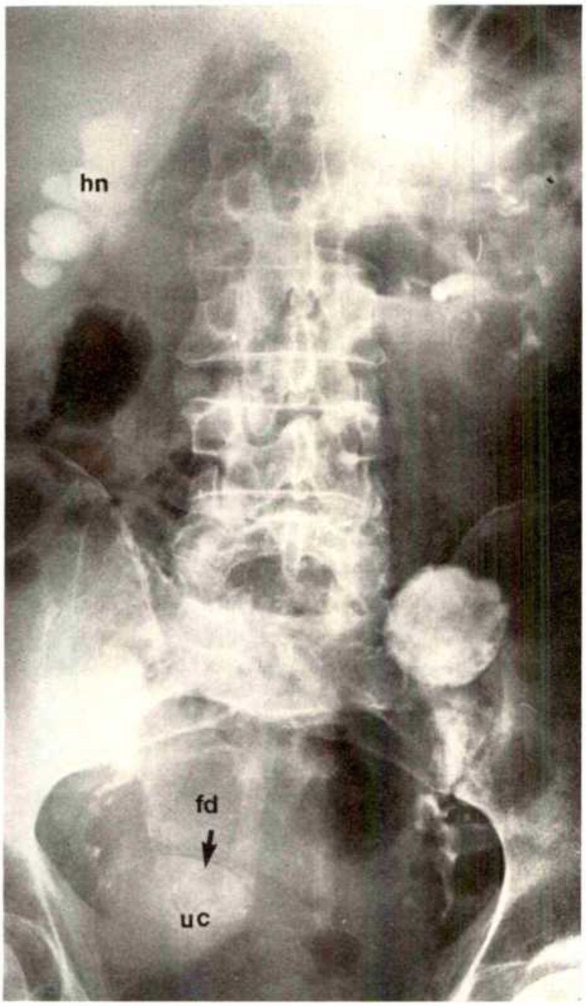


FIG. 1.

Twenty minute film from IV urogram series. hn = hydronephrotic (R) pelvicalyceal system; fd = filling defect; uc = uterocele.

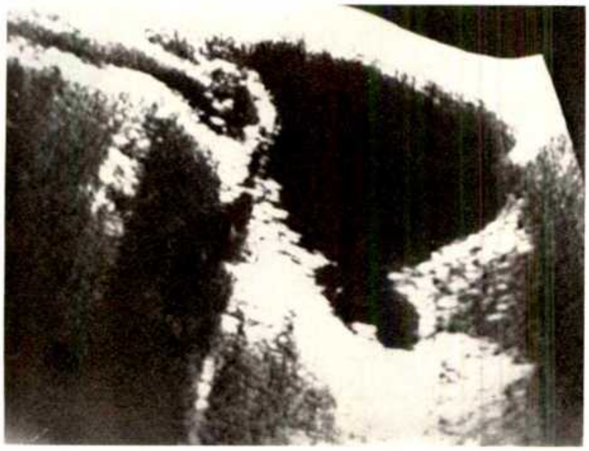


FIG. 2.

Longitudinal grey-scale ultrasound image.

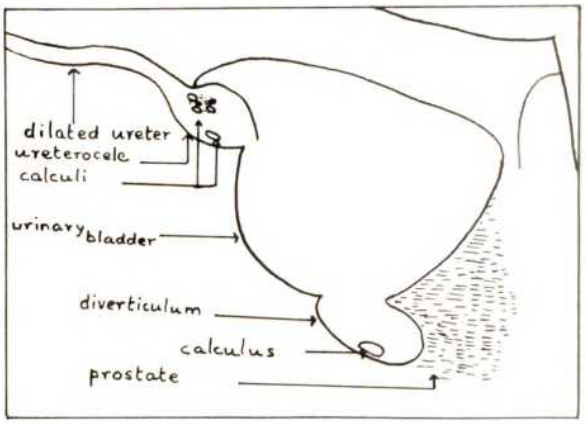


FIG. 3.

Explanatory diagram of Fig. 2.

1978, *British Journal of Radiology*, *51*, 1018–1019

also permit an anterior ultrasound approach to the region of the ureteric orifices.

ACKNOWLEDGMENTS

We wish to thank Mr. A. D. Jervis of the Hospital Photography Department for processing the reproductions, Mrs. J. Ridley for typing the manuscript and Dr. Anula Nikapota for Fig. 3.

REFERENCE

BAILEY, H., and LOVE, M., 1959. *A short practice of surgery.* 11th edn., p. 734.

Ultrasonic diagnosis of tuberculous peritonitis

By B. M. Gompels, F.R.C.R., and L. Gail Darlington, M.R.C.P.

Departments of Radiology and General Medicine, Epsom District Hospital, Dorking Road, Epsom, Surrey

(*Received April, 1978*)

Tuberculosis results in the notification of some 8000 cases per year and chiefly occurs in the elderly and immigrant populations. Clinical presentation of tuberculous peritonitis with fever, vomiting, constipation and ascites is not uncommon. Diagnosis is usually confirmed by Mantoux testing, paracentesis, liver biopsy and/or laparatomy. Paracentesis may, however, be unhelpful since ascitic fluid dilutes the mycobacterial population/unit volume, making the bacilli difficult to isolate.

Ascites is commonly encountered in routine ultrasonic practice. Proto, 1976, and Goldberg *et al.*, 1970 emphasize the *distribution* of ascitic fluid without mention of specific diagnostic features. A case is reported in which ultrasound led to an immediate diagnosis, enabled an ideal site for paracentesis to be chosen and protected the patient from further invasive procedures.

CASE REPORT

A 49-year-old travelling groom, born in Madras but having lived in the United Kingdom since 1950, presented with a four week history of vomiting and persistent, non-colicky, left abdominal pain. He was constipated and feverish with frequent bouts of sweating which necessitated a change of clothing at least once nightly. He had a dry, unproductive cough and had lost more than 8 kg in weight. On examination, he was a thin Asian male who did not appear to be particularly ill. Abdominal distension and ascites were present with a pyrexia swinging daily between 36° and 39°C. Preliminary investigations were unhelpful with an ESR of 10 mm/hour, a white cell count of $6500/mm^3$ and a serum alkaline phosphatase of 25 K.A. units. Chest and abdominal radiographs showed no detectable abnormality. A transverse ultrasound scan of the abdomen (Fig. 1) with a standard ultrasound apparatus* showed ascitic fluid, mainly in the right lower abdomen. Real time scanning† demonstrated fine, interlacing strands of more solid material within the ascitic fluid, passing from the bowel to the abdominal wall. This lattice-like pattern could not be reproduced with section scanning but fine strands are shown in Fig. 2 using the 5 MHz transducer.

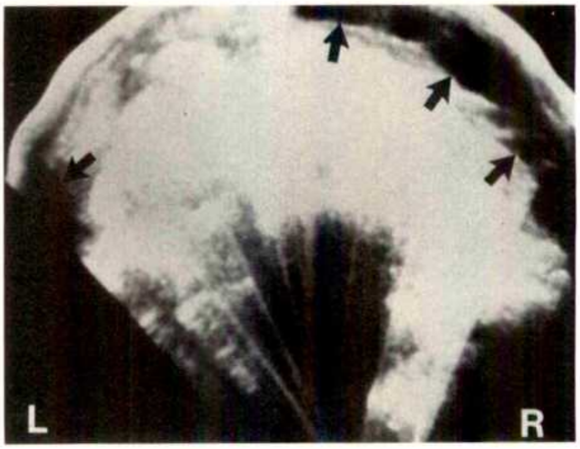


FIG. 1.

Transverse section of abdomen showing ascites (arrowed) predominantly in the right lower abdomen. The white areas represent matted loops of bowel.

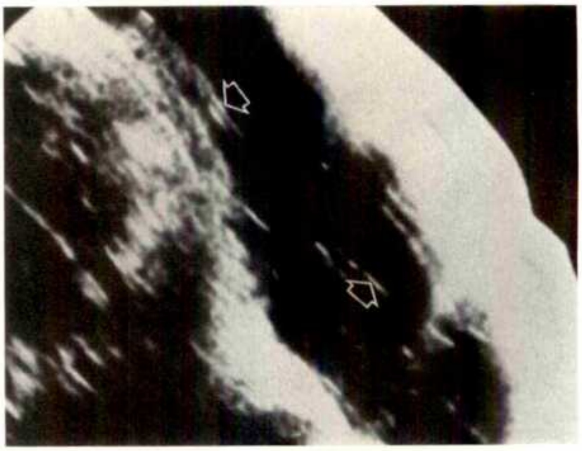


FIG. 2.

Enlarged view of ascitic fluid in right lower abdomen, using a 5 MHz transducer. The adhesions (arrowed) are shown as fine strands traversing the fluid.

---

*Diasonograph 4200 2.25 MHz 19 mm probe NE 4323; 5 MHz 13 mm probe. NE 4354.

†Toshiba Real Time Phased Array Sequential Scanner SAL 10A.

Straw-coloured, clear fluid was aspirated from the right lower abdomen from the region suggested by the ultrasound scan and the spun deposit revealed white cells consisting of 99% lymphocytes and also scanty acid and alcohol-fast bacilli. Treatment was started with Rifampicin, INAH and Ethambutol and the patient responded quickly and made an uneventful recovery.

DISCUSSION

In the presence of pronounced weight loss, wasting, anorexia, fever, enlarged liver and spleen and deranged liver function tests, Harrison (1977) considers the most common causes of ascites to be cirrhosis, carcinoma with peritoneal involvement, tuberculosis and hepatoma. Without ultrasound, diagnosis frequently requires peritoneal biopsy, peritonoscopy, splenoportography, or laparatomy.

Ultrasound will accurately detect small quantities of ascitic fluid which may be clinically unsuspected. With gross abdominal swelling the encapsulated fluid of an ovarian cyst can be differentiated from free ascitic fluid surrounding liver and loops of bowel. It is not usually possible to establish the causes or nature of the fluid unless associated pathology such as cirrhotic liver or pelvic tumour can be identified. Yeh and Wolf (1977) illustrate thick bands of tissue in malignant disease in which loops of small bowel appear to be stretched between mesentery and abdominal wall. Loculated ascitic fluid which may be seen in the frozen pelvis caused by cystadenocarcinoma of the ovary (Yeh and Wolf, 1977) may be confused with the solid and cystic components of the tumour.

Fine, delicate, interlacing and mobile strands seen in the case reported have not previously been described as an ultrasound finding but are consistent with the known pathological composition of tuberculous ascites with its high protein content and were probably composed of strands of deposited fibrin.

The different pattern of adhesions demonstrated by section scanning compared with real time phased array system is of interest. This is probably related to the direction and manner of propagation of the ultrasound beam from the static probe head.

CONCLUSION

The contribution of ultrasound scanning to the diagnosis of patients with ascites may not be restricted to anatomical assessment but may help to give an exact clinical diagnosis and to protect the patient from further invasive investigation.

REFERENCES

GOLDBERG, B. B., GOODMAN, G. A., and CLEARFIELD, H. R., 1970. Evaluation of ascites by ultrasound. *Radiology, 96,* 15–22.

HARRISON, T. R., 1977. *Principles of Internal Medicine.* 8th ed. Part 2, Section 5, 226 (McGraw-Hill, London.)

PROTO, A. V., 1976. A new concept of ascitic fluid distribution. *American Journal of Roentgenology Radium Therapy and Nuclear Medicine, 126,* 974–980.

YEH, H. C., and WOLF, B. S., 1977. Ultrasonography in ascites. *Radiology, 124,* 783–790.

Book review

Angiography of the human brain cortex. By G. Szikla, G. Bouvier, T. Hori and V. Petrov, 1977, pp. xxi+313, Springer-Verlag KG, Berlin $149.60.

This book deals with the relationship of specific blood vessels to particular cortical sulci and gyri and considers the reconstitution of cortical anatomy from the course of the cortical vessels.

It commences with a summary of the authors' methods of stereotaxic localization. The second chapter deals with three dimensional anatomical studies of the cortical sulci and gyri and the embryonic basis for the cortical pattern. Next stereotaxic dissection of each gyrus is described in specimens in which the arteries have been injected with a radio-opaque material; beautiful photographic and radiographic illustrations have been obtained and are reproduced. There follows correlation of the angiographic and anatomical aspects of individual sulci; this gives especially interesting data on the effects of the orientation of the sulcus on the projection of vessels in depth of the sulcus which explains the crossing of cortical vessels on routine angiograms.

The fifth chapter illustrates the application of the method to the derivation of cortical patterns in normal and pathological angiograms presented in stereotaxic projection. Finally, the sulcal vascular laminae are shown on conventional tomograms. The book is beautifully illustrated and contains the results of an immense amount of work. It shows that the authors' painstaking method will produce precise results and it has given interesting anatomical data, not previously emphasized. Many neuroscientists will wish to study these results. Although the method may be useful in relation to stereotaxic biopsy, it is difficult to see a major practical application in routine neuroradiology at present.

B. E. KENDALL.

1978, *British Journal of Radiology*, *51*, 1020–1022

Short communication

The double contrast meal—new high density barium sulphate powders

By W. B. James, F.R.C.R., F.R.C.A. (G.)
Department of Radiology, Southern General Hospital, Glasgow

(*Received January, 1978 and in revised form June, 1978*)

It is clear that there is continuing interest by radiologists in methods of carrying out double contrast barium meals (Saxton, 1977). It is also clear that many radiologists have been disappointed by the results obtained using methods described in the literature. I believe that there are two main reasons for this disappointment: (a) most writers have described rather elaborate, inflexible and time-consuming methods of examination; (b) the barium sulphate preparations currently used give poor mucosal coating. These two reasons are interrelated—poor barium sulphate suspension means that a longer contact with the mucosa is necessary to achieve even reasonable coating. Paralysing agents are thus used to delay gastric emptying in order to prolong the mucosal contact, to assist in uniform distension and to diminish unwanted peristalsis. These are desirable effects but the advantages are outweighed by the consequent

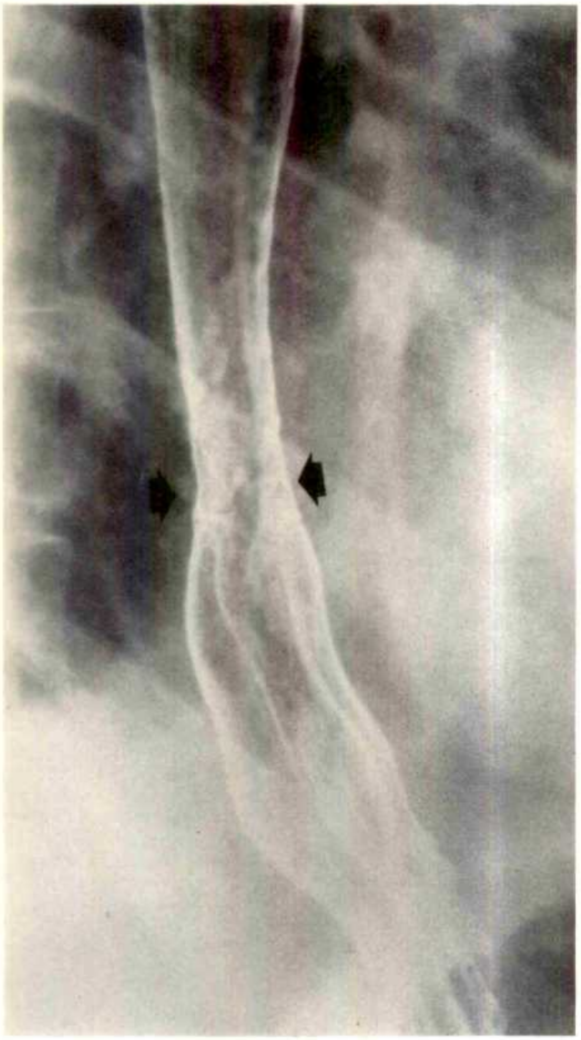


FIG. 1.
Moderate oesophagitis.

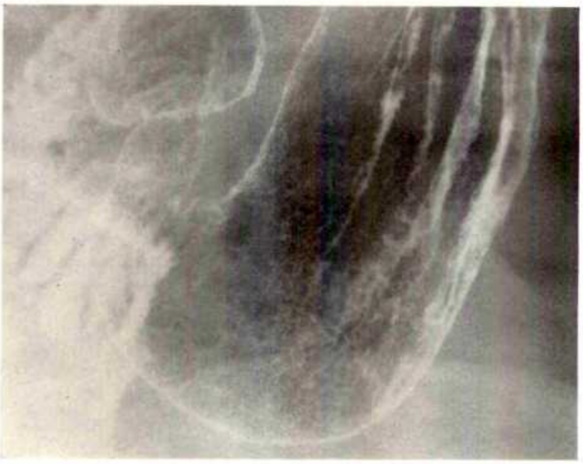


FIG. 2.
Areae gastricae patterns in body of stomach.

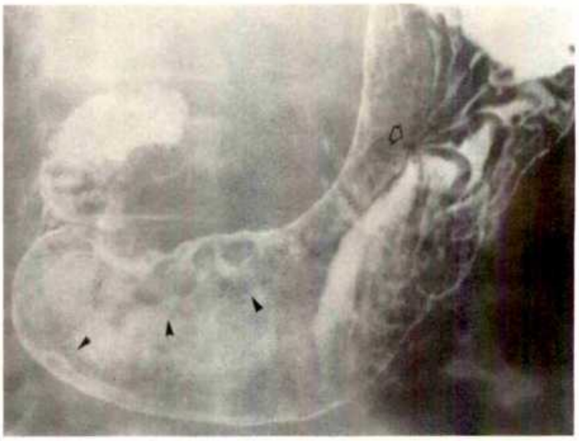


FIG. 3.
Healing ulcer posterior body. Multiple adenomatous polyps in antrum.

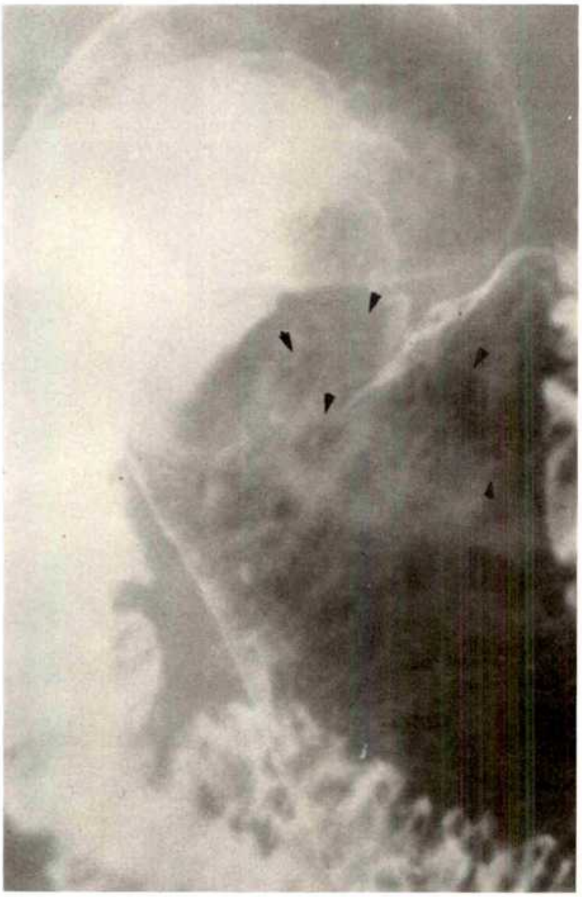


FIG. 4.
Multiple tiny antral erosions—erosive gastritis.

increase in time for examination which we have measured to be in excess of 50%. The other problem which has deterred many radiologists is the difficulty in getting consistently good mucosal coating using presently available barium sulphate suspensions even with paralysing agents. In general the quality of demonstration of the fine mucosal detail of the stomach—the areae gastricae pattern—using these suspensions is very poor. The same applies to coating of the duodenum. In the oesophagus fine mucosal detail is hardly ever demonstrated. It is astonishing that we know so little of the physical basis of mucosal coating by barium sulphate suspensions. It is likely that quality of coating is multifactorial and depends on (a) properties of the barium sulphate suspension itself such as size and shape of particles, method of suspension, radiographic density and viscosity and (b) on biological factors such as the amount and kind of fluid in the lumen of a viscus and the state of its mucosa and covering layer of mucus (MacKintosh and Kreel, 1977; James, 1978). Undoubtedly these factors vary in importance between different viscera. We believe that high quality upper gastro-intestinal examinations are best obtained using crushed natural barium sulphate powders containing rough particles with jagged edges having a size range from 0.5 μm to 30 μm (James, 1978). Uniform particles such as are obtained from precipitated barium do not give good results. Such coarse particle barium powder preparations have recently become commercially available (X-Opaque powder, E-Z-HD). They are suspended shortly before use and constitute a significant advance in performing high quality DC barium meals. We have used these now for more than two years and have abandoned the use of other preparations for upper gastro-intestinal examinations.

The preparation of these powders for use is important. It is very simple but to begin with should be supervized by the radiologist himself. 70 ml of water is added to approximately 300 g of the dry powder in a suitable shaker. The mixture is shaken vigorously for a mintue or so then stirred. This makes up to 150 ml of barium suspension and is enough for two patients. The suspension sediments rapidly—this is almost certainly one of its desirable properties as far as mucosal coating is concerned—and must be stirred again shortly before giving to the patient. Additional gas must be given for a good DC examination. This is best administered outside the barium room two or three minutes before the examination. Enough tablets or powder should be given to produce 200 to 400 ml of gas in the stomach. The patient is instructed not to eructate. Routine fluoroscopy of the chest is carried out in the usual way. At the same time the size of the gastric air bubble is checked. After some experience it will be clear as to whether or not enough gas has been given. If not, additional gas can be administered. The amount of gas necessary will vary with the volume of the stomach but it should stretch without obliterating the mucosal folds and the angle between fundus and body of stomach should be straightened. In general there is a direct relationship between the amount of gas and the amount of barium—the greater the distension the more barium must be used. Again the amount of barium becomes easy to judge after some experience. Usually between 70 and 100 ml is required. In the erect right anterior oblique position the patient is instructed to drink *rapidly* 70 to 100 ml of barium. The majority of patients swallow a considerable amount of air at the same time and high quality views of the air distended oesophagus are obtained after passage of the barium bolus. It is best not to ask the patient to stop breathing as this often causes the distended oesophagus to collapse. It is useful therefore to be able to expose films very rapidly and to use a short exposure time. The patient is then *immediately* lowered to the horizontal keeping on the left side. From the left lateral decubitus position the patient is moved rapidly through 360 deg turning to his left onto his face then quickly round onto the back and onto the left side again. These manoeuvres must be carried out as quickly as possible in order to produce rapid movement of the barium across the mucosal surface. The left lateral position is maintained for a short period to allow barium to drain from the antrum up to the fundus. The patient is then returned to the supine position. In the vast majority of patients good coating of the whole of the gastric mucosal surface is obtained with minimal entry of the barium into the duodenum. Suitable manoeuvres are then undertaken to demonstrate the whole of the mucosal surface of stomach and duodenum on film.

Personal examination of over 2000 patients in the last two years has shown that one can now recognize early mucosal changes in the oesophagus such as those seen in oesophagitis as well as demonstrating more clearly the mucosal changes in carcinoma. In the stomach areae gastricae are demonstrated in at least 90% of patients. The demonstration of small ulcers and scars—often in unusual situations—becomes common-place and the changes of erosive gastritis and other uncommon lesions are shown. The results in the duodenum are equally good. Examples of the technique are illustrated in Figs. 1–4.

Undoubtedly the accuracy of the radiologist will equal that of the endoscopist and the reporting of normality by the radiologist takes on a new significance. This is not surprising since this is truly a *mucosa* imaging technique—akin to endoscopy. All of this will be achieved in the same time as before. The techniques are thus suitable for routine application and especially suitable for the training of young radiologists who after a very short training period will produce high quality films for consultation.

The radiologist must now ask himself not whether it is desirable that he should adopt such a technique as that described but whether it is acceptable to continue to use outmoded and inaccurate methods.

REFERENCES

Saxton, H. M., 1977. Starting the double contrast barium meal. *British Journal of Radiology*, *50*, 610–612.

MacKintosh, C. E., and Kreel, L., 1977. Anatomy and radiology of the areae gastricae. *Gut*, *18*, 855–864.

James, W. B., 1978. Double contrast radiology in the gastrointestinal tract. *Clinics in Gastroenterology*, *7*, 397–430.

Book review

Myelography. Text book and atlas. By Ingar O. Scalpe and Ove Sortland, pp. 100, illus., 1978 (Oslo, Forlaget Tanum Norli a.s.), N.kr.98.00.

It is only since the introduction of contrast media with sufficiently low neurotoxicity to allow examination of the lower thoracic region, that water-soluble radiculography has been generally accepted in Great Britain and water soluble myelography has only recently become possible with the general release of metrizamide. The appearance of this short book dealing with the essentials of Metrizamide myelography is therefore most timely. It is written by two Norwegian neuroradiologists internationally well known, especially for their work with Metrizamide. In addition to more than five years of practical experience with this contrast agent, they have much wider experience of water-soluble radiculography using Abrodil and of myelography with iodophendylate and air and are therefore, in an ideal position to assess the merits of the new medium.

After a brief historical introduction and discussion of the indications for the procedure there is a very good and well illustrated description of the authors' technique for examination of each region. This is considered in detail and in the cervical region, examination using both lumbar and cervical puncture is discussed. Mention is also made of Metrizamide in computer assisted myelography.

Brief chapters deal adequately with absorption of Metrizamide from the subarachnoid space and its elimination, with adverse effects and with pre- and post-examination care.

The last chapter dealing with the merits and limitations of Metrizamide in the demonstration of the various pathological processes occurring in each region is well illustrated as an atlas and, though by no means comprehensive, it demonstrates well the merits of the medium. Finally, there is a good selection of references. The only unfortunate feature is the incorrect spelling of several English words, but this never interferes with easy appreciation of the authors' meaning.

The book is recommended as an authoritative introduction to myelography with water soluble contrast media and especially to radiologists who are embarking on the use of Metrizamide.

B. E. Kendall.

1978, *British Journal of Radiology*, *51*, 1023–1024 DECEMBER 1978

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

The neurotoxicity of misonidazole: pooling of data from five centres

THE EDITOR—SIR,

At the Gray Conference held at Cambridge in September 1977, all the clinical groups having experience in the administration of misonidazole (Ro–07–0582) to patients reported upon their findings. There was a general agreement that neurotoxicity—principally peripheral neuropathy—was the limiting factor in determining the amount of this promising radiosensitizing compound which could be given to patients. It was further agreed that a pooling of the clinical data would advance knowledge as to the safe conditions for use of misonidazole in radiotherapy.

Case records were submitted in a simple tabular form by the Regional Radiotherapy Centre, Mount Vernon Hospital (89), Department of Radiology—Division of Radiation Oncology, Alberta (33), Strahlentherapeutische Klinik und Institut für klinische Strahlenbiologie, Vienna (22), University Department of Oncology and Radiotherapy, Cambridge (19) and division of Radiation Oncology, University of California, San Francisco (14) to make a total of 177 in all.

The data from the five centres were placed in the Rad 8 computer in the Radiotherapy Centre at Mount Vernon Hospital. To the actual data recorded by each centre concerning each case (age, height, weight, dose, number of doses, duration of treatment) the computer was programmed to add derived parameters (surface area, average dose, average interval between doses, the total dose divided by weight and the total dose divided by surface area). A Fortran IV computer program was written to generate, upon command, scatter diagrams for any pair of parameters. The scatter diagrams can be created with either linear or log scales which automatically cover the range of values. These may be seen on a visual display unit and then printed out as required.

A first examination of the data demonstrates a relationship between the incidence of peripheral neuropathy and the dose given (Fig. 1). No patients suffered neuropathy at a total dose

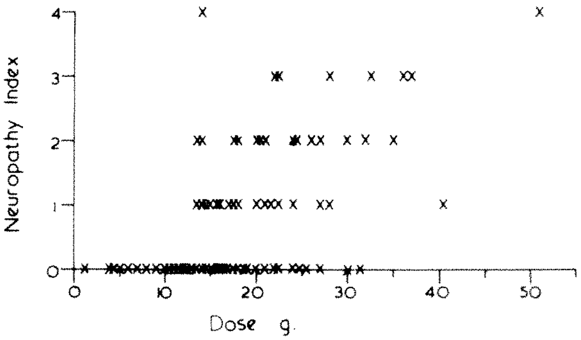


Fig. 1.

A scatter diagram showing the relationship between neurotoxicity and total dose of misonidazole given. Symptoms due to neurotoxicity are graded—0 = none, 1 = slight, 2 = moderate, 3 = severe and 4 = convulsion (Saunders *et al.*, 1978).

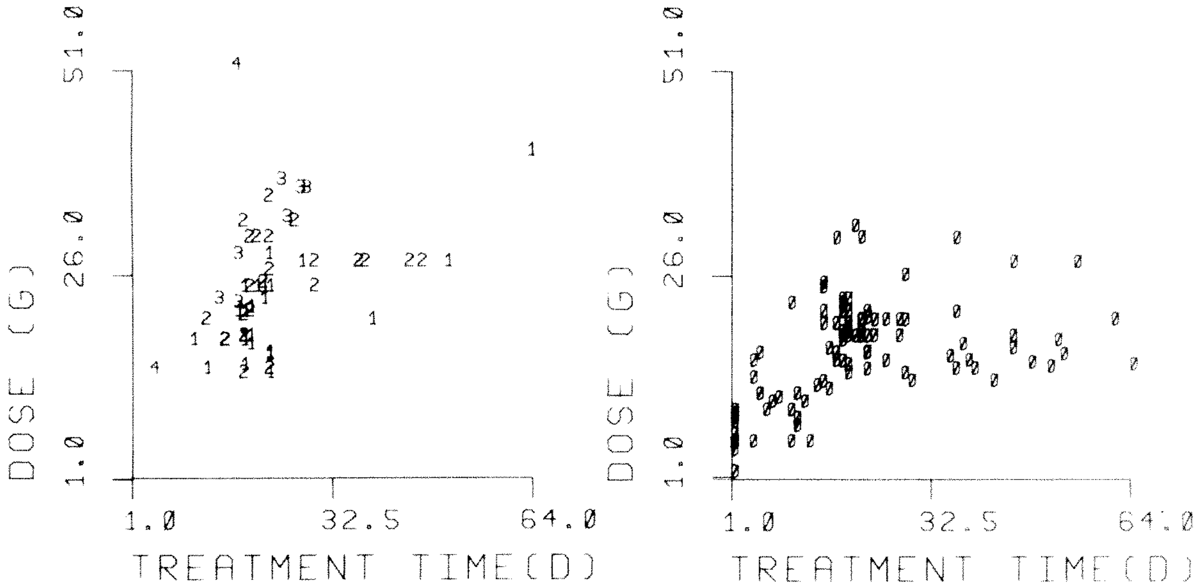


FIG. 2.

A scatter diagram showing the relationship between the total dose of misonidazole given with the duration of treatment. Those suffering neurotoxicity (58 patients) are shown on the left and those who did not (118 patients) are shown on the right. The digit plotted in each case is the individual's "neuropathy index".

1978, *British Journal of Radiology*, *51*, 1024–1025

below 13.5 g and there was an indication that the severity was directly related to actual dose given.

There was some evidence for increased incidence of neuropathy in younger patients, but this seemed negated by a greater trend for younger patients to be given higher doses. This may have been so because, in the earlier work with misonidazole, single and therefore limited doses were given to patients with advanced disease and these patients tended to be in an older age group.

Examining the scatter diagrams for the correlation of treatment time and dose, we gained an impression of less neuropathy in the patients given longer overall treatment times (Fig. 2). The total dose of misonidazole is obviously the most important factor in the incidence of neuropathy. To obtain more information about the influence of other factors such as body weight, surface area, overall time, fractionation of dose, etc. we need to divide the cases into groups having similar doses. This will become more practical as a larger number of cases are recorded in the data bank.

This collaborative effort demonstrates the benefit which may be achieved by a pooling of information. We hope that other centres working with misonidazole will join us in building up this data bank concerned with the drug.

We wish to thank Professor J. F. Fowler and Professor G. E. Adams for their advice and encouragement and Roche Products Limited for the continued supply of misonidazole.

Yours, etc.,

S. Disch,
M. I. Saunders,
P. Anderson.

Regional Radiotherapy Centre,
Mount Vernon Hospital,

R. C. Urtasun,

Department of Radiology,
Division of Radiation Oncology,
Alberta,

K. H. Karcher,
H. D. Kogelnik,

Strahlentherapeutische Klinik und Institut fur
klinische Strealenbiologie,
Vienna,

N. Bleehen,

University Department of Oncology and Radiotherapy,
Cambridge,

T. L. Phillips,
T. H. Wasserman.

Division of Radiation Oncology,
University of California,
San Francisco.

REFERENCE

Saunders, M. I., Dische, S., Anderson, P. and Flockhart, I. R., 1978. The neurotoxicity of misonidazole and its relationship to dose, half-life and concentration in the serum. *British Journal of Cancer*, *37*, *Suppl. III*, 268–270.

Misonidazole (Ro-07-0582) sensitizes mice to convulsions induced by hyperbaric oxygen or pentylenetetrazol

The Editor—Sir,

Hypoxic radiosensitizers are being used in clinical trials with increasing enthusiasm. Early results with metronidazole (Flagyl) and misonidazole (Roche-07-0582) have been encouraging and suggest that these agents may enhance the effectiveness of radiation against hypoxic tumour cells in man as they do in animals. Some radiotherapists, reasoning that misonidazole and hyperbaric oxygen both act towards the same desirable end, have irradiated patients using both treatments simultaneously. Some of these attempts have resulted in convulsions, the incidence being much higher than would be anticipated for either agent alone (Dische, 1977).

This limited clinical experience does not permit one to decide whether or not the combination is contraindicated, because the numbers are small, the patients involved were quite ill, and, although it is rare, either agent alone has caused convulsions. We undertook, therefore, to resolve the question experimentally using mice. Female CBA/J mice (Jackson Labs., Bar Harbor, Maine), chosen for their sensitivity to hyperbaric oxygen (Hill *et al.*, 1968), were injected intraperitoneally with 1 ml of either normal saline or misonidazole dissolved in saline (1 mg per g body weight). One hour later, when serum misonidazole levels were at their peak (Hirst *et al.*, 1978), the animals were placed in hyperbaric oxygen (4 atmospheres absolute). Exposure to hyperbaric oxygen was carried out in a chamber of our own design and manufacture (Steier, 1970), using a five minute purge, pressurization and depressurization at 1 atmosphere/min, and a three litre/min throughflow of gas during the exposure. In all experiments, the endpoint was time to onset of a clearly definable and sustained convulsion.

Misonidazole clearly sensitized the mice to convulsions caused by hyperbaric oxygen (Fig. 1). The drug hastened the onset of convulsions and increased the proportion of animals that convulsed: 100% of the misonidazole-treated mice convulsed within 12 min compared with only 58% of the controls within 60 min (the longest time observed). Misonidazole alone caused no convulsions at the dose used. The results indicate that a dose of misonidazole which is in the range used for radiosensitization in mice lowers their threshold to convulsions when in high pressure oxygen.

Next, we asked whether misonidazole would enhance convulsions induced by a central nervous system stimulant, pentylenetetrazol (PTZ, Metrazol). The rationale for this experiment was that pentylenetetrazol exactly mimics certain features of the hyperbaric convulsive syndrome (Bean *et al.*, 1966; Harris and van den Brenk, 1968), although it differs from oxygen in not producing long-term paralytic brain damage (van den Brenk and Harris, 1970).

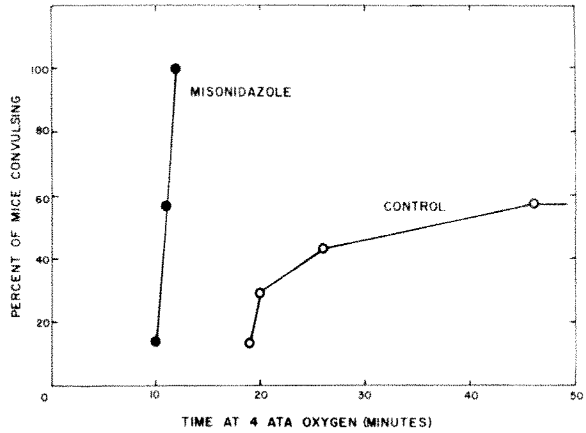


Fig. 1.

Effect of misonidazole (RO-07-0582) on convulsions induced by oxygen at 4 atmospheres absolute (4 ATA). CBA/J mice received misonidazole (1 mg/g body weight) or saline 1 hour before hyperbaric exposure was begun. Each point represents a cumulative score (*i.e.* total percentage of mice that had convulsed by the time shown) and each curve represents 12–15 mice.

Correspondence

Mice received an intraperitoneal injection of either saline or misonidazole (1 mg per g body weight) and then, one hour later, a challenge dose of PTZ (1 mg in 0.1 ml, intraperitoneally). The control mice convulsed at a mean (± s.e.) of 168 ± 13 seconds (range, 120–210 seconds) after PTZ was injected, whereas the mice that had been treated with misonidazole 1 hour before convulsed much earlier, at a mean of 69 ± 9 seconds (range, 45–90 seconds). We conclude that misonidazole lowers the threshold for convulsive activity caused by this CNS stimulant just as it does for hyperbaric oxygen.

There is relatively little information as to the mechanism(s) by which any of these agents act on the CNS. Both hyperbaric oxygen and PTZ act on autonomic centres and stimulate neuroendocrinological pathways associated with the sympathetic system (van den Brenk and Harris, 1970). PTZ probably increases cellular permeability in the CNS, causing partial depolarization of neuronal membranes and a consequent decrease in neuronal recovery time (Franz, 1975). Oxygen at high pressure may have similar effects (Bean *et al.*, 1966), but its mechanism of action remains obscure. Misonidazole also has direct effects on neuronal membranes, causing a decrease in nerve conduction velocity via unknown mechanisms (Hirst *et al.*, 1978). How these facts and similarities are to be interpreted in terms of the results we have presented in this paper is uncertain.

We conclude that hyperbaric oxygen must be used cautiously in patients who also receive misonidazole. The same caveat would presumably hold for other sensitizers of related chemical structure. Perhaps further studies of the type reported here, particularly using various adrenergic antagonists and other blocking agents, may help to elucidate misonidazole's neurotoxic mechanism(s) and lead to pharmacological means of avoiding or controlling such side-effects.

Yours, etc.,
J. W. HARRIS,
D. C. SHRIEVE.

Department of Radiation Oncology,
University of California Medical Center,
San Francisco,
California 94143 USA.

ACKNOWLEDGMENT

This work was supported by NCI Grants Nos. CA 17227 and CA 20529. We acknowledge with thanks the technical assistance of J. Meneses.

REFERENCES

BEAN, J. W., ZEE, D., and THOM, B., 1966. Pulmonary changes with convulsions induced by drugs and oxygen at high pressure. *Journal of Applied Physiology*, *21*, 865–872.
DISCHE, S., 1977. Personal communication.
FRANZ, D. M., 1975. Central nervous system stimulants. In *The Pharmacological Basis of Therepeutics*, eds. L. Gilman and A. Goodman, pp. 362–363 (Macmillan Publishing Co., Inc., New York).
HARRIS, J. W., and VAN DEN BRENK, H. A. S., 1968. Comparative effects of hyperbaric oxygen and pentylenetetrazol on lung weight and non-protein sulfhydryl content of experimental animals. *Biochemical Pharmacology*, *17*, 1181–1188.
HILL, G. B., OSTERHOUT, S., and O'FALLON, W. M., 1968. Variation in response to hyperbaric oxygen among inbred strains of mice. *Proceedings of the Society for Experimental Biology and Medicine*, *129*, 697–698.
HIRST, D. G., VOJNOVIC, B., STRATFORD, I. J., and TRAVIS, E. L., 1978. The effect of the radiosensitizer Misonidazole on motor nerve conduction velocity in the mouse. *British Journal of Cancer*, *37* (*Suppl. III*), 237–241.
STEIER, H., 1970. Hyperbaric chamber for cell suspensions and small animals. *Laboratory Practice*, *19*, 1035–1036.
VAN DEN BRENK, H. A. S., and HARRIS, J. W., 1970. Brain damage in rats following pentylenetetrazole and high pressure oxygen. *Experientia*, *26*, 1327–1328.

Iocarmide (Biligram) studies in man

THE EDITOR—SIR,

Bell *et al* (1978) in their very interesting study of different methods of injections of iocarmide, point to a failure rate of 25% using bolus injection of 30 ml and only a moderate demonstration in another 25%. At the Newcastle General Hospital, bolus injection is routinely used in all non-jaundiced patients. The authors' figures seemed surprisingly high and this prompted a limited retrospective study to assess frequency of failure in this department.

Patients were referred between January 1977 and April 1978. The selection and radiological assessment was carried out in the same way as the above authors. Only patients with known serum bilirubin level of more than 25 mmol/l and alkaline phosphates of 300 IU/l were excluded. The results are as shown in Tables I and II.

Our figures represent a failure rate of less than 3%, statistical comparison* with those of Bell *et al.* indicate a significant difference ($p=0.015$). Comparing our results using bolus injection with Bell's drip infusion rate of 3 mg/kg/min also shows a significant difference ($p<0.001$), our bolus injection results having a higher proportion of patients in the "good" category.

Fisher's exact test for a 2 × 3 table were used in preference to Bell's χ^2—tests as the numbers involved are rather small, *p*-values obtained from Fisher's exact test of Bell's published results are very similar.

It would appear that our success with the bolus method is at least as good as, if not better than, Bell's drip infusion rate of 3 mg/kg/min. Our bolus technique yields good films in 82.8% as opposed to 35% using Bell's optimal infusion method. A failure rate of only 3% in our results would seem to be acceptable and indicate that it is suitable for clinical use and, in addition, would be preferable because it is less time-consuming and simpler. Since the study was retrospective I am not in a position to comment with regard to patients reactions other than to state that no major side effects have been recorded.

TABLE I

NEWCASTLE BOLUS INJECTION RESULTS V. PUBLISHED BOLUS INJECTION RESULTS

	Failed	Moderate	good
Newcastle	1	5	29
Bell *et al*, (1978)	5	5	10

$p=0.015$.

TABLE II

NEWCASTLE BOLUS INJECTION RESULTS V. PUBLISHED 3 MG INFUSION RESULTS

	Failed	Moderate	Good
Newcastle	1	5	29
Bell *et al.* (1978)	0	13	7

$p= <0.001$.

---

*The statistical analysis were kindly carried out by Mr. A. B. Heath from the Department of Medical Statistics, University of Newcastle upon Tyne.

The marked difference in the results of these two small series indicates that a much larger prospective study needs to be done to establish relative merits of the bolus or infusion methods used to demonstrate the biliary system.

Yours, etc.,
B. D. SHAH.†

Department of Radiology (main),
Newcastle General Hospital,
Newcastle upon Tyne.

REFERENCE

BELL, G. D., FRANK, J. M. FAYADH, P. L. C. SMITH, and I. KELSEY FRY., 1978. Ioglycamide (billigram) studies in man. Radiological opacification of the bile duct. A comparison of a number of different methods. *British Journal of Radiology*, *51*, 191–195.

---

†Now at Department of Radiology, Royal Victoria Infirmary, Newcastle upon Tyne.

Reduction of X-ray tube output during life

THE EDITOR—SIR,

Mr. Addy's letter helps to demolish a piece of folklore (Addy, 1978). Normal bulb deposits do not significantly alter the inherent filtration of an X-ray tube. Simple calculations suggest that the amount of tungsten evaporated from a conventional X-ray tube filament is unlikely to form a deposit thicker than 0.3 μm (equivalent to about 10 μm of aluminium at normal diagnostic beam qualities). The greatest problem with bulb deposits is their effect on the insulating properties of the glass, which sometimes leads to instability or destruction of the tube. A fallacious demonstration of its insignificance to the transmission of radiation is to hold a well filmed bulb in front of a lamp—the light transmitted is surprisingly great.

The lack of change in HVL of the output from a tube with a well worn anode can be understood by comparing it to the dried bed of a lake. The flat islands will produce radiation of the normal quality; radiation produced in the crevices will be very strongly filtered and make only a very small contribution to the total output so that the first HVL is essentially that of the radiation produced on top of the islands.

Yours, etc.,
G. WATERS.

Machlett X-Ray Tubes (Great Britain) Limited,
East Lane,
Wembley, HA9 7PR.

REFERENCES

ADDY, J. W., 1978. Increased filtration due to tungsten deposits inside the envelopes of X-ray tubes. *British Journal of Radiology*, *51*, 397.

Scheduling of radiological equipment maintenance and generation of archival records using a mini-computer

THE EDITOR—SIR,

The scheduling of radiological equipment maintenance has become increasingly difficult as equipment has grown more complex and more heavily used. At the same time, licencing, accrediting and regulatory agencies increasingly require archival records of maintenance procedures performed on radiological as well as other equipment. In the case of radiotherapy equipment, concern extends not only to the traditional dose-delivery calibration record but to such items as coincidence between the optical and radiation fields, interlock tests, excess dose-rate indicators, area monitors, etc. Often the records are required both on-site and at some administrative centre so that "hardcopy" duplication is essential.

We have developed a detailed description of our maintenance tasks and established how often each task should be performed over a 20-year period. Originally, we kept track of the tasks on a pegboard (Karzmark and Huisman, 1965), later on a magnetic board and currently with the aid of a Digital Equipment Corporation PDP-11/50 time-shared mini-computer. Our regularly scheduled maintenance tasks for three accelerators, three simulators and other equipment occur at intervals of one, two, four, eight, 12 and 26 weeks. The modulo points for the tasks on the various accelerators are staggered in sequence in order to equalize the work load for the single afternoon and evening reserved each week for maintenance. In practice we hold to a repetitive pattern of 13 job mixes for each half-year. Accordingly, we have programmed our computer to select and print out the proper job mix for each weekly maintenance date. Along with the job mix, we print the date and reserve space for exceptional information we wish to record on the maintenance record. With this list in hand, we check off the individual items and the person responsible for the maintenance signs the record. We keep this "hardcopy" on file at a central file in our department for examination by ourselves and by interested agencies.

Yours, etc.,
C. J. KARZMARK,
P. A. HUISMAN,
D. C. RUST.

Department of Radiology,
Stanford University School of Medicine,
Stanford,
California 94305, USA.

REFERENCE

KARZMARK, C. J., and HUISMAN, P. A., 1965. A programmed maintenance system for complex radiological equipment. *British Journal of Radiology*, *38*, 474–475.

SI units and dimensions of NSD, CRE and TDF

THE EDITOR—SIR,

Although I welcome anything which may ease the transition to SI units in radiological work, I am afraid Iyer (1978) is wrong both in the dimensions of the quantities he discusses and in his understanding of what constitutes an SI unit.

It has to be said that *NSD* (nominal standard dose) has been none too clearly defined. Orton and Ellis (1973) say "Ellis (1967) proposed that the tolerance dose for normal tissues (*D* rads) could be related to the overall treatment time (*T* days) and the number of fractions (*N*), by the expression:

$$D=(\mathrm{NSD})\,.\,(T)^{0\cdot 11}\,.\,(\mathrm{N})^{0\cdot 24} \quad \ldots\ldots\ldots\ldots\ldots(1)\text{''}$$

(The italics are as used in the original publication.) They go on to say, "The constant of proportionality in the equation is termed the nominal standard dose, or NSD." And later, "For practical purposes, it is expedient to consider NSD simply as a number . . .". However, I think it follows from the name and from his suggested unit "ret" (rad equivalent therapy) that Ellis intended *NSD* to be a particular absorbed dose. If *T* in equation (1) is taken to be a number (*i.e.* the numerical value of time expressed in days) then *NSD* has the same dimensions as *D*. More precisely we should write the quantity equation:

$$D=NSD\,(t/t^{\theta})^{y}\,N^{0\cdot 24} \quad \ldots\ldots\ldots\ldots\ldots(2)$$

where t is time and t^{θ} is a standard value of time. When t^{θ} is equal to one day y takes the value 0.11. But the term in brackets is always a pure number and as N is a non-dimensional quantity NSD has the same dimensions as D. NSD should therefore be expressed in the same unit as D, and in SI the unit is the gray.

The cumulative radiation effect (*CRE*) presents further dimensional problems. It has been inadequately defined (Kirk *et al.*, 1971) by a mixed quantity and number equation. Kirk *et al.* (1971) say "The CRE is a generalised form of the empirical function NSD . . ." which would imply that it has the same dimensions as *NSD*, namely those of absorbed dose. But they also say ". . . it (CRE) has the unit 1 rad day$^{-0.11}$ . . .". I think the introduction of day$^{-0.11}$ comes about by mistaking T in equation (1) for time when it is really the numerical value of time expressed in days. *CRE* should therefore have the same dimensions as absorbed dose and be expressed in the SI unit, gray.

Iyer (1978) is correct in his statement that the adoption of SI will reduce *TDF* factors (Orton and Ellis, 1973) by a factor of $100^{1.538}$ or 1191. If the scaling factor of 10^{-3} introduced by Orton and Ellis is dropped at the same time *TDF* will change overall by a factor of only 0.839. The unit, however, will be Gy$^{1.538}$ without the added day$^{-0.169}$ mentioned by Iyer.

My other point is that if an SI unit, such as the gray, is taken and renamed the "get" (gray equivalent therapy) for a special application, the "get" is *not* an SI unit. It would not be an SI unit until it has been approved by the General Conference on Weights and Measures (GCWM), and I see little prospect of such approval being given. Neither would I regard it as being necessary. We will have to be more careful in future to state the quantity we are measuring and not to rely on the unit to imply the quantity. In radiological work we have several quantities with the same dimensions as absorbed dose, namely specific energy, absorbed dose index, and kerma, so a statement of a number of grays also requires a statement of which of the above four quantities is intended. This is not a new requirement brought about by the introduction of SI, as it is already necessary when using the rad which is also a unit applicable to all four of these quantities.

Unfortunately, SI has acquired some of the attributes of a religion, in that many converts and disciples insist on dogma that was not required by the original prophet. As I have no wish to be included with these people I should point out that the GCWM has occasionally permitted more than one special name for an SI unit. Thus the derived SI unit, s^{-1}, has the special name hertz for use with periodic phenomena, and becquerel for use with radioactivity. Also, at the time of writing, the Consultative Committee on Units has sent forward with approval to the GCWM a proposal that the J kg^{-1}, which already has the special name, gray, for the quantities mentioned above, should have the special name, sievert, when used for the quantities dose equivalent and dose equivalent index. But there must be a limit to the number of special cases the radiological community puts forward to the GCWM, and we should not need to invent a new named unit whenever a new quantity is proposed.

Yours, etc.,

J. R. Greening.

Department of Medical Physics and
Medical Engineering,
Royal Infirmary,
Edinburgh EH3 9YW.

REFERENCES

Ellis, F., 1967. Fractionation in radiotherapy. In *Modern Trends in Radiotherapy*, eds. Deeley and Wood, vol. 1, pp. 34–51 (Butterworth, London).

Iyer, P. S., 1978. NSD, CRE, TDF and SI units. *British Journal of Radiology*, *51*, 473.

Kirk, J., Gray, W. M., and Watson, E. R., 1971. Cumulative radiation effect. Part 1: fractionated treatment regimes. *Clinical Radiology*, *22*, 145–155.

Orton, C. G., and Ellis, F., 1973. A simplification in the use of the NSD concept in practical radiotherapy. *British Journal of Radiology*, *46*, 529–537.

Forthcoming events

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (*i.e.* April 20, for June edition).
Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Symposium on Chemotherapy for Solid Tumours

Norfolk and Norwich Hospital, January 17, 1979. Papers to be presented on chemotherapy for lung, head and neck, testicular, bladder and breast cancer. Enquiries to: Dr. A. W. Jackson, Consultant Radiotherapist, Norfolk and Norwich Hospital, Norwich, Norfolk.

Radiobiology Meetings

The following meetings are scheduled at the Institute: "Radiation chemists talk to biologists", January 19, 1979. "Preview of papers for the International Congress, Japan", April 20, 1979.

Titles and preferably brief abstracts of papers proffered for the January meeting should reach Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, by December 14, 1978.

Further information can be obtained from the General Secretary, B.I.R. (01-935 6237).

Problems of Benign and Malignant Bone Tumours

A joint evening meeting organized by the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, to be held on Friday, January 19, 1979, at the Royal Society of Medicine, London.

Speakers: Dr. Mary Catto, Dr. P. Jacobs, Mr. D. R. Sweetnam and Dr. G. E. Flatman.

Further information: contact the Royal Society of Medicine.

Radiation Biology for Part I F.R.C.R. (Radiotherapy and Oncology)

An intensive course in Radiation Biology will be held from January 22–26, 1979 inclusive. It is primarily intended for radiotherapists in training but it is also open to other students of radiation biology and experimental oncology. Lectures and demonstrations will be given by the staff of the Paterson Laboratories.

Details from: Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX.

Clinical Oncology Symposium on Thyroid Cancer

The Royal College of Radiologists will be holding a multi-disciplinary symposium on January 26–27, 1979. It will be held at 66 Portland Place, London W1N 4AD and is intended for senior registrars, consultants and research workers. Selected topics on the subject of thyroid cancer will be reviewed by authoritive speakers from the United Kingdom. The registration fee is £25.

Full details of the symposium can be obtained from the Meetings Secretary, Royal College of Radiologists, 28 Portland Place, London W1N 4DE.

New Radiopharmaceuticals Including ^{123}I

An all day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on Wednesday, February 14, 1979 at the Middlesex Hospital Medical School.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Imaging in Nuclear Medicine

An evening meeting to be held on Thursday, February 15, 1979 at The British Institute of Radiology, 32 Welbeck Street, London, W1, organized jointly by The British Institute of Radiology, the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology).

Further information contact the General Secretary, The British Institute of Radiology.

Workshop on the use of Computerized Tomographic Scanners in Radiotherapy

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proffered papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

1979 The British Institute of Radiology Annual Congress

The 37th British Institute of Radiology Annual Congress and Scientific Exhibition will be held at the Middlesex Hospital Medical School on April 26–27, 1979. Included in a programme of invited papers on diagnosis, therapy, radiological physics and nuclear medicine topics will be the Presidential Address by Mr. W. M. Ross entitled *The Institute, yesterday and tomorrow*, and the Silvanus Thompson Memorial Lecture by Professor G. E. Adams on *Past, present and future of hypoxic cell sensitizers*.

Details and registration from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Mackenzie Davidson Memorial Lecture

To be given by Dr. G. B. Schofield, Medical Officer, British Nuclear Fuels Ltd., on *Biological control in a plutonium production facility* at The British Institute of Radiology, 32 Welbeck Street, London, W1 on Thursday, May 17, 1979.

Eighteenth Annual Leo G. Rigler Lecture and Convention on Pediatric Radiology

Sponsored by the Tel-Aviv University Sackler School of Medicine, Section of Diagnostic Radiology, and the Municipal Government Medical Centre, Tel-Aviv, Yaffo, Departments of Diagnostic Radiology is being held at the Accadia Hotel, Herzlia-on-Sea, May 8–10, 1979. The Rigler Lecturer will be John A. Kirkpatrick Jr., M.D., Professor and Radiologist-in-Chief, Children's Hospital Medical

Center, Boston, Mass. The guest faculty will include Drs. W. E. Berdon, N. Cremer, J. S. Dunbar, K. D. Ebel, S. G. Gerzoff, B. A. Girdany, C. A. Gooding, H. Grosman, J. L. Gwinn, M. T. Gyepes, H. J. Kaufmann, R. S. Lachman, J. C. Leonidas, A. E. Oestreich, F. N. Silverman, E. B. Singleton and J. Spranger. The other member of the Faculty will include lecturers from the academic staff of the four medical schools in Israel.

Registration fee: $150.00; residents $100.00.

For further information kindly contact Professor S. Schorr, Ichilov Hospital, Tel-Aviv, Israel.

Note: The 18th Annual Rigler Lecture and Convention on Pediatric Radiology in Israel will follow the meeting of the European Society for Pediatric Radiology in Koeln, May 3–5, 1979.

INTERNATIONAL SYMPOSIUM ON INTERVENTIONAL RADIOLOGY

An E.A.R. Symposium, organized by the Portuguese Society of Radiology and Nuclear Medicine, will be held May 30–June 2, 1979 in the Algarve, Portugal.

Proposed sessions include vascular therapy; selective embolization and management; catheter implantation in chemotherapy and percutaneous treatments; ultrasonic guiding techniques and nuclear imaging as a guiding technique for biopsy and fluid aspiration.

For further information contact the Portuguese Society of Radiology and Nuclear Medicine, 123, 1.° Esq., Avenida Elias Garcia, Lisbon 1, Portugal.

INTERNATIONAL COURSE IN CHEST RADIOLOGY

International Course in Chest Radiology and other aspects of chest disease, Stockholm, Sweden, June 11–13, 1979.

Organized by the *Fleischner Society*, a non-profit organization in memory of Felix Fleischner, Harvard University, Boston.

Information and application forms from: Björn Nordenström, M.D., Professor of Radiology, c/o Reso Congress Service, S-105 24 Stockholm, Sweden.

NUCLEAR CARDIOLOGY

A workshop organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on June 20, 1979 at the Institute House.

Further information contact the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The L.H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Obituary

Captain T. W. Barnard, O.B.E. 1885–1978 London – Madras – Sheffield

In November 1942 Captain Barnard took charge of a tiny office in the Sheffield Royal Infirmary as Secretary of the Sheffield National Centre for Radiotherapy. From that time until he retired in 1964 his influence on the development of radiotherapy services in Sheffield was immense. In 1942 radiotherapy services were in a scattered chaos with a minimum of treatment facilities because of war-time dispersal. Twenty years later megavoltage therapy had been developed, a comprehensive isotope facility was in being, a wide-ranging independent medical physics department was established, and building had started on the new radiotherapy hospital. The role of an administrator in such developments is easily undervalued. Captain Barnard had a vigour, a vision, a stubbornness and a self-confidence which in retrospect can be seen clearly as a major influence in shaping radiotherapy in Sheffield, even if during the course of that shaping various authorities may sometimes have felt beaten down by his cavalier disregard of "proper procedures".

In 1946 T.W.B. began negotiations with MIT about building a 2 MeV Van de Graaf generator for Sheffield. He persuaded a local benefactor to give enough money to house the machine and to place an order with the newly formed High Voltage Engineering Co. of Boston to build the first commercial model. He it was who organized the rescue of the treatment department from its moorland hut and housed it in a large house in town, and who later repeated the process of organizing another temporary radiotherapy department when construction of foundations for the new teaching hospital overwhelmed the existing site. It was Captain Barnard who obtained a large house nearby to set up the Regional Medical Physics Department in 1960—and who over many years during the planning of the new radiotherapy hospital conducted a running battle with some success against higher authorities who would have cut down corridor widths, room sizes and so on.

The development of radiotherapy services in Sheffield after the war is a testimony to Captain Barnard's administration. It is astonishing to realize that in 1942, when it began, T.W.B. was 58 and his real achievements in radiology were elsewhere and earlier. The Sheffield period really came after a "retirement".

T. W. Barnard joined the staff of the X-ray department of the London Hospital, Whitechapel in 1908. His work there must have taught him two important lessons—first the possibility of getting good results from poor facilities if you persist, and second the need to give proper attention to radiation protection. His colleagues included three who died of X-ray cancers. He had unprotected tubes to use but he achieved some fine and some exciting radiography.

When war came in 1914 Barnard had command of a London Cadet Battalion. 1916 found him with HM Forces in India as a commissioned officer in charge of radiology in the Colabar War Hospital in Bombay. Here he found an empty room without power supply but with packing cases full of X-ray equipment evacuated from the Galipoli campaign. His first task was to persuade his Indian colleagues that X-ray pictures were possible in spite of crashes and sparks arising from high tension leaks in the humidity of Bombay.

In 1920, a year when T.W.B. became a member of the BIR, he accepted a temporary appointment to organize a Radiological Service in Madras. He remained there until 1941 as Chief Officer of Radiology Services for the Madras Government with supervision of all X-ray services in an area three times that of England and a population of 50 millions. During that period Captain Barnard opened some twenty new X-ray departments in the state and developed the service in the Madras General Hospital and Medical College as a major teaching centre for South India. Madras General Hospital had had its first X-ray outfit in 1900. T.W.B. organized a Temporary Institute in 1922 in some rooms in the hospital and twelve years later finally established the Madras Government Institute of Radiology, to his surprise named after him on the day of the official opening in March 1934. By any standards the Barnard Institute of Radiology was an enormous achievement. There was nothing like it in India or in South East Asia, and not much like it in the USA or Great Britain at that time. It was a two storey building round a courtyard where playing fountains formed part of the air-conditioning plant of the X-ray diagnostic department. Its therapy unit housed a 400 kV apparatus, three 200 kV units, two superficial and two contact sets. It had a radium department including a radon plant for supplying radon for up-country hospitals. It had a physics department and laboratory, a physiotherapy department and a clinical photography unit. With its protected walls of locally-made brick loaded with barium it had a layout so far in advance of its time that for a generation it remained the outstanding radiological centre of South East Asia. Captain Barnard remained Director of the Institute until he left India; under his guidance through courses for the Diploma of Medical Radiology and for Certified Radiological Assistants the Institute was a training ground for medical people and radiographers who have served all over India and the East. Captain Barnard was President of the Board of Examiners for both diplomas.

Captain Barnard's interests were by no means exclusively radiological. He was, for instance, for twenty years associated with the Madras Boy Scouts Association, first as treasurer and then as Deputy Chief Commissioner. He was a keen collector of art objects of the Orient and was understandably proud of the great beauty of his collection.

All those who have had association with "The Cappy" will remember with appreciation a vigorous administrator who gave enormous help to young radiologists, to radiographers and to physicists and who in Madras and Sheffield made a contribution to radiology and radiotherapy of truly giant proportions. We remember him with affection and gratitude and offer our condolences to his widow and daughter.

H. MILLER.

Correspondence (*continued*)

Scheduling of radiological equipment maintenance and generation of archival records using a mini-computer.
C. J. Karzmark, P. A. Huisman and D. C. Rust
SI units and dimensions of NSD, CRE and TDF.
J. R. Greening

Forthcoming events.	1028
Obituary: Captain T. W. Barnard	1030

Book reviews

Biological effects of ^{224}Ra. Benefit and risk of therapeutic application	952
Dictionary of abbreviations in medicine and the health sciences	962
An atlas of normal developmental roentgen anatomy	973
Encyclopaedia of urology V/1 supplement, diagnostic radiology	985
Invasive radiologic diagnostic procedures	991
A radiographic index	1010
Angiography of the human brain cortex	1019
Myelography. Text book and atlas	1022

Journal review

Environmental International	980

APPEAL

A permanent home for British radiology

The Appeal Committee

Sir Jan Lewando, CBE *(Chairman)*
Dr. Julian Bloom
The Lord Hunt of Fawley, CBE
Mr. Kevin Hughes
Sir Peter Kerley, KCVO, CBE
Professor L. F. Lamerton
Sir Thomas Lodge
Dr. J. F. Loutit, CBE, FRS
Professor W. V. Mayneord, CBE, FRS
Professor J. H. Middlemiss, CMG
The Lord Penney, OM, KBE, FRS
Sir Edward E. Pochin.
Sir John Read
Mr. C. F. E. Shakerley
Dr. S. Cochrane Shanks, CBE
Professor Sir David Smithers
Professor R. E. Steiner
Dr. Herman D. Suit
Dame Janet Vaughan, DM
Professor Sir Brian Windeyer
The Lord Zuckerman, OM, KCB, FRS
Professor G. H. du Boulay *(Appeal Co-Ordinator)*
The President of the Institute and Appeal Executive Committee members

Funds are needed to secure a new permanent home for the British Institute of Radiology at 36 Portland Place, London, W1, next door to the Royal College of Radiologists

Donations and ideas to:
Appeal Co-ordinator BIR, 32 Welbeck Street, London W1M 7PG
(01–935 6237)

The British Journal of Radiology

Contents

Page

Current thoughts on fast neutron therapy. Mackenzie Davidson Memorial Lecture, November 17, 1977. 943
W. Duncan

Obstructive jaundice and portal vein calcification. 953
R. L. Mackenzie, H. R. Tubbs, J. W. Laws, J. L. Dawson and R. Williams

Is pancreatogram interpretation reliable?—a study of observer variation and error. 956
A. Reuben, A. L. Johnson and P. B. Cotton

Lateral subluxation of the atlas in rheumatoid arthritis. 963
R. W. Bunton, D. M. Grennan, D. G. Palmer and R. T. D. de Silva

A comparison of grey-scale image recording systems. 968
Hylton B. Meire and Pat Farrant

Reduction of radiation dose to patients in xeroradiography. 974
T. H. E. Bryant and W. L. Julian

Limitations of the single sample tracer method for determining glomerular filtration rate. 981
B. E. Chatterton

The influence of size and radiopharmaceutical concentration ratio on the detection of abnormalities in clinical radionuclide imaging. 986
A. V. Lakshmanan, P. Sharp and J. Mallard

The effect of chronic reductions in the arterial partial pressure of oxygen on the radiation response of an experimental tumour. 992
D. W. Siemann, R. P. Hill and R. S. Bush

The effect of vascular occlusion on the thermal sensitization of a mouse tumour. 997
Sally A. Hill and Juliana Denekamp

Instrumental and technical notes. 1003
- Automatic numbering punch for radiation protection films.
  K. P. Goulding and F. W. Walton
- Improvement of scanner performance by subtraction of Compton scattering using multiple energy windows.
  D. J. Waggett and B. C. Wilson

Case reports. 1011
- Obstructive jaundice caused by cavernous transformation of the portal vein.
  H. C. Meredith, I. Vujic, S. I. Schabel and P. H. O'Brien
- Tuberculosis of the breast.
  A. Ward, S. Field and R. E. C. Collins
- Spasm of the superior mesenteric artery complicating methysergide maleate therapy.
  P. Lowe, A. Hoiseth and T. Nordshus
- Grey-scale ultrasound demonstration of ureterocele and hydroureter.
  V. L. B. Nikapota and M. I. Wray
- Ultrasonic diagnosis of tuberculous peritonitis.
  B. M. Gompels and L. Gail Darlington

Short communication. 1020
- The double contrast meal—new high density barium sulphate powders.
  W. B. James

Correspondence. 1023
- The neurotoxicity of misonidazole: pooling of data from five centres.
  S. Dische, M. I. Saunders, P. Anderson, R. C. Urtasun, K. H. Karcher, H. D. Kogelnik, N. Bleehen, T. L. Phillips and T. H. Wasserman
- Misonidazole (Ro-07-0582) sensitizes mice to convulsions induced by hyperbaric oxygen or pentylenetetrazol.
  J. W. Harris and D. C. Shrieve
- Iocarmide (Biligram) studies in man.
  B. D. Shah
- Reduction of X-ray tube output during life.
  G. Waters

(Continued, inside back cover)

Printed in Great Britain by Lund Humphries
London and Bradford
Published by THE BRITISH INSTITUTE OF RADIOLOGY
32 Welbeck Street, London W1M 7PG

ISSN 0007-1285
12700